‘Clinical profile, prognostic factors and outcomes in anti Tuberculous drug induced liver injury’

A dissertation submitted in partial fulfilment of the requirements for DM (Branch IV, Gastroenterology) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in August 2011.

Certificate

This is to certify that this dissertation titled 'Clinical profile ,prognostic factors and outcomes in anti Tuberculous drug induced liver injury' is a bonafide work done by Dr.Joby Augustine in partial fulfilment of rules and regulations for DM(Branch IV – Gastroenterology) examination of The Tamil Nadu Dr MGR Medical University ,to be held in August 2011.

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Introduction

Drug induced liver injury (DILI) is a problem of increasing significance. It is a long standing concern in the treatment of tuberculosis (TB). Pathogenesis and types of anti-TB DILI ranges from hepatic adaptation to hepatocellular injury. Hepatotoxicity is the most serious side effect of anti tuberculosis treatment (ATT) and it causes substantial morbidity as well as mortality and can diminish the efficacy of treatment. Anti-TB DILI can present as asymptomatic transaminase elevation to serious hepatotoxicity in the form of hepatic failure-Acute, Sub acute or acute on chronic liver failure. Systematic steps for prevention and management of TB DILI are recommended.

The incidence of ATT induced hepatotoxicity varies from 8-30% in different studies [43, 44]. More serious liver disease induced by ATT occurs in 0.01% to0.03% of patients. Several risk factors for anti-TB DILI have been described, including age, sex, race, pre-existing liver disease, extent of tuberculosis, alcohol consumption, low body mass index, acetylator status, use of hepatotoxic drugs, and a high dosage of ATT in relation to body weight.

Isoniazid – induced hepatotoxicity usually occurs soon after the start of ATT, but can still occur at any later time point during treatment. Continuation of isoniazid despite symptoms has been associated with a severe clinical course and fatal outcome. Pyrazinamide hepatotoxicity usually occurs after longer periods of treatment but again this is not a rule. Isoniazid can result in acute liver failure (ALF) but pyrazinamide more often leads to sub acute hepatic failure (SAHF). In patients in whom liver function recovers after

discontinuation of ATT, the drugs can often be restarted by sequential introduction along with frequent monitoring of liver function tests (LFT).

International guidelines issued by the American Thoracic Society, the British Thoracic Society and European Respiratory Society Task Force all state that baseline determination of liver function should be carried out before ATT is started in patients with TB. Regular monitoring of LFT is advocated in patients with underlying liver disease or known risk factors for liver disease.

Aims

1) To study the clinical profile and to assess the prognostic factors and outcome of anti-TB Drug induced liver injury

2) To assess risk factors for ATT induced liver failure (compared to ATT induced hepatitis).

Review of literature

The liver plays a major role in metabolism of drugs and hence is susceptible to its toxic and deleterious effects. It is an important cause of liver failure in the West and East. It is an important cause for asymptomatic transaminitis as well as acute liver failure. The mortality in acute liver disease due to drugs is approximately 10% [2]. Since there is no specific test for confirmation, the diagnosis mainly rests on the suspicion and causality assessment and then on discontinuation of the suspected drug following which liver function tests gradually improves. DILI is also a serious concern for the pharmaceutical companies. The safety and toxicology issues are the major concerns in clinical trials.

Definitions and Importance

Drugs are a relatively common cause of liver injury. Drug induced liver injury(DILI) is defined as abnormalities of liver biochemical test levels, particularly an increase in the serum alanine aminotransferase (ALT), alkaline phosphatase, or bilirubin level, to more than twice the upper limit of normal.[1] .Over 300 drugs have been implicated in drug induced liver injury , but only 50 are reliably described. Some drugs cause predictable dose dependent liver injury (acetaminophen and methotrexate) where as in most cases it is unpredictable. These unpredictable DILI are mostly either idiosyncratic or immune mediated. In most cases of DILI, liver biopsy tells us about the extent of injury rather than the cause. Hence the diagnosis is often based on i) temporal relationship between the drug ingestion and liver injury ii)exclusion of other causes, iii)the presence of extra hepatic manifestations of drug hypersensitivity(immune allergic reaction),iv) findings on liver biopsy.[2]

Epidemiology of Drug-Induced Liver Injury.

DILI is an important cause of withdrawal of drug from the market.[3,4,5]. The epidemiology of DILI is poorly understood because of the limited active and passive reporting and surveillance systems in place and the lack of standardized criteria for its diagnosis. There are many retrospective and prospective studies describing the incidence and risk factors associated with DILI in the literature.. The risk of DILI in a population ranges from 1 in 10,000 to 1 in 100,000 people exposed [6].DILI accounts for 5%-10% of patients admitted because of acute hepatitis [7-10] . A French study has shown the incidence of DILI to be 14per100, 000 patients.[3] This is definitely an under estimation as many cases as subclinical. Many herbal and dietary supplements are also reported to cause DILI especially in South East Asia [11].

Drugs are the most common causes of fulminant hepatic failure in the West[12-14].In the West, acetaminophen has been reported to be the single most common cause of acute liver failure where as in South Asia anti tuberculous (anti-TB) treatment is the most common cause of drug induced liver failure[15].Idiosyncratic drug reactions are presumed to account for 13% of liver failure in US and 17% in Sweden.[3,12,13].Early recognition of DILI is important so that continued exposure can be avoided thus preventing severe liver dysfunction. Studies have shown that prognosis for patients with drug induced liver failure is poor with mortality ranging from 60%-80% without liver transplantation.[12-14]. The US ALF study group has shown that idiosyncratic drug injury (13%) was second only to acetaminophen overdose (39%) following the analysis of their registry during 1998-2001[16]. In a recent study published from Northern India, Ramesh Kumar et al has reported that the mortality in patients of Anti Tuberculous treatment(ATT) induced acute liver failure

(ALF) is 67%[15].In an another study from Southern India , Devarbhavi H et al showed an overall mortality of 21% in anti-TB DILI.[17]. Agal S et al noted mortality of 16.6% in ATT induced hepatitis in their study from Western India [18].Drug induced ALF accounts for approximately 20% of ALF in children, most common aetiology being acetaminophen (15%), followed by anti tuberculous drugs and anti epileptic therapy.

Over the last decade, the three prospective registries that significantly enhanced our knowledge of DILI are the Regional Registry of Hepatotoxicity in southern Spain, the U.S. Acute Liver Failure Study Group (ALFSG), and the Drug-Induced Liver Injury Network (DILIN). The importance of these registreries is that they provide an opportunity to study the mechanisms, aetiology, associated risk, case fatality in DILI and helps to find out preventive measures for these serious and potentially fatal drug reactions. There is a lack of of reporting of DILI from developing countries including the Indian subcontinent. An ageing population, increasing co-morbidities, and diseases such as tuberculosis, HIV, epilepsy which are more prevalent in developing countries, (which are all treated with multiple drugs,) results in an overall increase in DILI in developing countries.

There is a paucity of data regarding DILI from the India although we have many case reports of ATT induced hepatitis. In a recent study,(in a retrospective analysis of consecutive collected data of patients with DILI, seen over a 12-year period) Devarbhavi .H et al described that DILI resulted in significant overall mortality (17.3 %).Anti Tuberculous Drugs (ATD), anti-convulsants, sulphonamides, and olanzapine were the leading causes of DILI. Although DILI was common in males, more females developed fulminant hepatic failure. The principal finding of that series was an overall mortality of 17.3% and 21.5 % mortality for anti-TB DILI. ATT was the major cause of DILI accounting for 58 % of cases, followed by anti-epileptic drugs, which accounted for 11.2 % of DILI.[17]. Although

amoxicillin- clavulinate or penicillin group of drugs are the common drugs in Western series (> 50%), in their series four-drug anti-tuberculous agents was the commonest cause. Another population-based study from Spain that included 33 cases of anti-TB DILI reported mortality of 22.7% [19]. Contrary to earlier reports this study did not show old age or female gender as risk factors for DILI.In another study published form AIIMS, Ramesh Kumar et al concluded that ATT-ALF constituted 5.7% of ALF at their centre and was associated with a high mortality rate [15]. Because the mortality rate was so high, determining which factors are predictors is less important. A high proportion of patients had consumed ATT empirically, which could have been prevented. Singla R et al in their study had concluded that older age, poor nutritional status including baseline hypoalbuminaemia were independent predictors of occurrence of anti-TB DILI.[20]

Causality assessment of drug induced liver injury

DILI is always a differential diagnosis for work up of patients with jaundice or abnormal LFT.Causality assessment of DILI can be difficult as there are no specific diagnostic markers or tests. Mostly it is the temporal association and course of the liver tests after withdrawal of drug that helps in the diagnosis. Exclusion of other aetiologies is also equally important. There are many prospective registries in the West. The first model for DILI causality assessment was prepared by the Council for International Organisation of Medical Sciences (CIOMS)-known as the Roussel Uclaf Causality Assessment Model (RUCAM) [21]. The RUCAM was initially tested in a case control study with positive rechallenge as cases. The authors finally chose a cut off of 5 and excluded rechallenge as it was a part of the case definition. The sensitivity, specificity, positive predictive value and negative predictive value were 86%, 89%, 93% and 78% respectively. Another scoring system developed by two Hepatologists from Portugal was Maria &Victorino Score which

was named after them. [22] But it is more stringent, specific and requires a positive rechallenge which can be detrimental sometimes. The RUCAM scoring system which is validated and used more frequently including the present study is mentioned below

RUCAM(CIOMS) Causality Assessment of a Drug in a case of Drug Induced Liver Injury

1 Enzyme pattern	Hepatocellular			Cholestatic or mixed		
Exposue	Initial	Subsequent	pts	Initial	Subsequent	pts
Time from drug start(d)	5-90	1-15	+2	5-90	1-90	+2
	<5or>90	>15	+1	<5or>90	>90	+1
Time from drug stop(d)	≤15	≤15	+1	≤30	≤30	+1
2 Course	Difference between- peak ALT and ULN			-peak ALP/bilirubin and ULN		
After drug stop	Decrease ≥50%in 8d		+3	Decrease ≥50%in≤ 180d		+2
	Decrease ≥50%in 30d		+2	Decrease<50%in< 180d		+1
	Decrease ≥50%in> 30d		0	Persistence/increase/no info		0
	Decrease<50%in> 30d		-2			
3 Risk factor	Ethanol: yes		+1	Ethanol/pregnancy:yes		+1
	Ethanol: no		0	Ethanol/pregnancy:no		0
Age	≥55					+1
	<55					0
4 Other drugs	None or no information					0
	Concomitant drug with compatible time to onset					-1
	Concomitant drug known as hepatotoxin and with compatible time to onset					-2
	Concomitant drug with e/o of its role in this case (+ve rechallenge or validated test)					-3
5Competing causes:Group1:Recent HAV,HBV, HCV,biliary obstruction,alcohol,recent hypotension, GroupII:complications of underlying disease,clinical or biological context suggesting CMV,EBV or herpes virus infection.				All causes of GrI/II ruled out The 6 causes of GrI ruled out 5or 4 causes of GrI ruled out <4causes of GrI ruled out No drug cause highy probable		+2 +1 0 -1 -3

6 Previous information on hepatotoxicity of the drug Reaction labelled in the product characteristics Reaction published but unlabelled Reaction unknown			+2 +1 0
7 Rechallenge Positive	+3	Positive	+3
Compatible	+1	Compatible	+1
Negative	-2	Negative	-2
Not done or not interpretable	0	Not done or not interpretable	0

Causality assessment model of RUCAM

Highly probable	Score >8
Probable	score6-8
Possible	score 3-5
Unlikely	score 1-3
Excluded	score≤0

Even after defining causality assessment models there are several limitations. These are not popular in paediatric DILI and routine use is not recommended. The classification of the injury into hepatocellular, cholestatic or mixed depends on the value of alkaline phosphatase which is highly variable in growing children [23].They use medicines less frequently than adults. Assessing causality in patients with underlying chronic liver

disease is intrinsically more difficult. Also when multiple drugs are involved it is often difficult to point out one single agent as the causative agent.

Metabolism of Drugs and Mechanisms in drug induced liver injury

The liver metabolizes virtually every drug or toxin introduced in the body. Most drugs are lipophilic.There are three phases in drug metabolism. Phase 1reaction involves oxidation or hydroxylation of the drug/metabolite which can result in toxic intermediates, e.g. -the metabolite of acetaminophen is *N* -acetyl-p-benzoquinone-imine (NAPQI).This is mediated via - CYP-450 enzymes ,located in the smooth endoplasmic reticulum. At least 50 enzymes have been identified which grouped into10 of which groups 1, 2, and 3 are being the most important in drug metabolism. Phase *2*- occur within or outside the liver. They involve conjugation with a moiety (i.e., acetate, amino acid, sulphate, glutathione, glucuronic acid) to facilitate excretion from the hepatocyte.Drugs with high molecular weight may be excreted in bile and the kidneys excrete the smaller molecules.Phae 3 is a energy-dependent process in which parent molecule, or its metabolites, or conjugates are transported into bile [1]

The initial process in the pathophysiology of DILI is the disruption of the hepatocyte. Covalent binding of the drug metabolites results decrease in ATP levels, leading to actin disruption. Disruption of the transport proteins in canalicular membrane can results in interruption of bile flow. Interruption of transport pumps (MRP-3) prevent the excretion of bilirubin .Cytolytic T-cell activation results in multifaceted immune response and apoptosis of hepatocytes [24] . This results in mitochondrial permeability transition which leads to inhibition of beta-oxidation resulting in decreased ATP production. TNF apha-trigger the cascade of intracellular caspases 3, 6 ,7 and 9 resulting in apoptosis. Toxic metabolites excreted in bile may cause injury to the bile duct epithelium also [25].

There are two types of DILI -1) Intrinsic or predictable drug reactions, 2) Idiosyncratic (metabolic idiosyncratic and Immunoallergic) drug reactions. The classic example of dose related and predictable DILI is acetaminophen. In this liver injury occurs after a short latent period (hours) and is characterized histologically by zonal necrosis or microvesicular steatosis.Idiosyncratic metabolic drug injury is defined as the susceptibility of rare persons to hepatotoxicity in conventional doses which is usually safe. This results from genetic or acquired differences in drug metabolism or canalicular secretion, mitochondrial defects, or cell death receptor signalling pathways. Here the latency varies from 7 days -1 yr.In Immuno allergic type, the immune system mediates the response to a drug. It is characterised by fever, rash, and eosinophilia and short latency period of 1-4 weeks E.g.: Phenytoin.

Risk Factors for drug induced liver injury

1) Genetic Factors-Atopic patients are at increased risk of drug induced hepatitis.Many genetic factors determine the drug-activating and antioxidant pathways**,** encode pathways of canalicular bile secretion and modulate the immune responses, tissue stress responses, and cell death pathways. Familial predisposition to adverse hepatic drug reactions has been reported (e.g -valproic acid and phenytoin) .Inherited mitochondrial diseases are risk factors for valproic acid–induced hepatotoxicity .Pattern of liver injury could be influenced by genetic determinants. Class II HLA haplotype is linked to cholestatic or mixed liver damage for some drugs like Amox-clav and Ticlopidine.

2) Age-DILI is more common in adults than in children, the exceptions being valproic acid (<3yrs), Reye's syndrome. Hepatotoxicity due to INH, Mox-clav, Halothane, Diclofenac, and Troglitazone are reported to be more in people who are above 55 yrs. Also in older age

cholestatic or mixed patterns of DILI are said to be more common.[6] DILI cases in children are generally mild, but paediatric DILI patients have the potential to progress to ALF.

3) Gender -Conflicting results have been reported in various studies. Some studies have shown an increased risk in females especially with drugs like Nitrofurantoin, Diclofenac, or Minocycline .But as recent review found that female sex was not a specific risk factor for developing DILI [26]However it has been observed that females are prone for hepatocellular pattern of DILI and hence a worse outcomes including ALF and higher mortality [27].

4) Concomitant exposure to other drugs-Patients taking multiple drugs are more likely to experience an adverse reaction than those who are taking one agent. Cytochrome P450 - mediated metabolism of the drugs results in multiple toxic intermediates. And these alter the disposition of drugs by reducing bile flow or competing with canalicular pathways for biliary excretion.

5) Previous drug reactions-Increases the risk of reactions to the same drug and also to some other agents. Previous reaction to the same drug is a major risk factor for severe DILI. Cross-sensitivity between drugs are also reported, e.g. haloalkane anesthetics, erythromycins, phenothiazines and TCA,INH and PZA, sulfonamides and some NSAIDs.

6) Alcohol-Increases the risk and severity of Acetaminophen,INH, Niacin hepatotoxicity, and Methotrexate induced hepatic fibrosis

7)Nutritional status- Obesity increases the risk of halothane hepatitis, NASH and hepatic fibrosis in persons taking methotrexate or tamoxifen .How ever there is no indication that body mass index (BMI) has significant influence on the risk, pattern, severity, or outcome of DILI [27] Some Indian studies have shown malnutrition as a risk factor for INH hepatotoxicity [20].

8) Pre-existing liver disease-Pre-existing liver disease is a critical determinant ofMethotrexate induced hepatic fibrosis .Chronic hepatitis B and HCV infection or HIV/AIDS increases the risk of liver injury during ATT, HAART therapy, NSAID, Myeloablative therapy, anti androgens.[28]

Patterns of DILI

The patterns of drug induced liver injury is divided into 3 categories based on the recommendations of the Council for the International Organisation of Medical Science(CIOMS) namely-hepatocellular ,cholestatic and mixed [21].Most of the patients presenting with hepatocellular DILI tend to be younger and a higher incidence of ALF was observed and hence Liver transplantation was offered to them frequently ,where as those with cholestatic/mixed pattern tend to be older age group in whom it was precluded because of many reasons. However, in a prospective study conducted by Ibanez et al, similar case fatality was observed in acute hepatocellular and cholestatic liver injury [29].

CIOMS consensus criteria for terminology in drug induced liver injury[21,30]

Terminology	Criteria
Hepatocellular injury	Isolated increase in ALT > twice normal or ALT/ALP≥5
Cholestatic injury	Isolated increase in ALP>twice normal or ALT/ALP≤2
Mixed injury	ALT and ALP are increased and 2<ALT/ALP<5
Acute injury	Above changes present for <3 months
Chronic injury	Above changes present for >3 months
Chronic liver disease	This term is used only after histologic confirmation

Prognosis in acute drug induced liver injury (DILI)

Hyman Zimmerman, the pioneer in DILI studies observed that the combination of hepatocellular injury associated with jaundice was associated with a mortality rate of 10%-50% for different drugs involve. Hy's rule is defined as a DILI with serum alanine aminotransferase (ALT) greater than 3 times the upper limit of normal along with s.Bilirubin more than 2 times the upper limit is associated with mortality of more than 10% [3].This was accepted by the US FDA for monitoring hepatotoxicity in clinical trials. The Hy's rule has been validated in different studies. Andrade et al observed mortality of 11% in patients with hepatocellular injury and jaundice [31].Devarbhavi H et al noted mortality of 26% in patients with DILI and icterus. [17]

The majority of patients with symptomatic acute drug induced liver injury (DILI) are expected to completely recover with supportive care after cessation of the offending drug. Milder episodes of DILI that may be unrecognized. It is also expected that these patients recover without residual clinical, laboratory, radiological, or histological evidence of liver disease. Even in presence of icterus majority of patients will recover clinically. However, the prognosis of patients with severe DILI who progress o acute liver failure (ALF) with coagulopathy and encephalopathy is usually poor. In most Western countries, acetaminophen overdose is the most frequently identified aetiology of ALF. But the prognosis is generally better in acetaminophen-induced liver failure patients treated with N-acetylcysteine than in ALF patients with idiosyncratic DILI (i.e., 60 to 80% versus 20 to 40%, respectively, in the absence of transplantation.). In the largest prospective series of U.S. ALF patients with idiosyncratic DILI, only 25% recovered once encephalopathy developed [16]. In the same

study, only advanced degree of encephalopathy at admission predicted mortality where as age ,sex and ethnicity were not. Recently, the U.S. Acute Liver Failure Study Group demonstrated that intravenous N-acetylcysteine therapy may benefit patients with ALF due to DILI, hepatitis B, and other aetiologies, particularly in those with early-stage encephalopathy [32]. But empiric use of corticosteroids in ALF due to DILI is not recommended due to the lack of benefit in previously reported studies. In view of poor prognosis, all patients with severe DILI should be referred to a centre with liver transplant facility. Age, bilirubin, aspartate aminotransferase (AST), and prothrombin time have been proposed as predictors of mortality. Bjornnson et al concluded age, AST, and bilirubin as independent predictors of poor outcome [33].O' Grady *et al.* reported the association of increased age, bilirubin, and coagulopathy with poor outcome in a small number of patients with idiosyncratic non-paracetamol, non-halothane DILI patients with fulminant hepatic failure [34].

Role of liver biopsy in DILI

The role of liver histology in the diagnosis and management is unclear. It may be useful in the setting of positive auto antibodies and persistently abnormal LFT.There is no pathgnomonic hall mark in histology. Certain histologic patterns can suggest DILI.These include zonal necrosis ,micro vascular steatosis,mixed hepatocellular and cholestatic pattern, disproportionate necrosis as compared to clinical picture, destructive bile duct lesions, prominent neutrophils and eosinophils(>25% of inflammatory cells),and hepatic granuloma formation [35].Severe hepatic necrosis is associated with 85% mortality. Studies have found that both peripheral and hepatic eosinophilia on biopsy are associated with a favourable outcome [19]

Anti Tuberculous drug induced liver injury(anti-TB DILI)

Despite progress in antimicrobial chemotherapy over the past 50 yrs, tuberculosis (TB) remains a major cause of illness and is the greatest infectious cause of death worldwide. Globally a total of 9.2 million new cases and 1.7 million cases of deaths from TB were reported in 2006 [36].World Health Organization estimated that prevalence of TB in India was 299 per 100,000population accounting for about one fifth of global figure. Mortality from TB in India is 28 per 100,000 population making it a major public health issue.ATT DILI is generally defined as a rise in ALT or AST more than five times the upper limit of normal in any patient or more than twice the upper limit of normal in the presence of symptoms or s.bilirubin more than twice the upper limit of normal in any patient taking hepatotoxic ATT regimen [18, 37, 38].

With modern anti-tuberculous treatment plus directly observed therapy, short course (DOTS),more than 85% detected cases of TB can be successfully treated. However treatment related adverse events are commonly encountered, especially within the first few weeks of therapy and anti-tuberculous drugs are one of the commonest groups of drugs that results in idiosyncratic hepatotoxicity world wide[16,39,40].The most frequent side effects of anti tuberculous treatment are hepatotoxicity, skin reactions, gastro intestinal and neurological disorders [41].Analysis of data from US FDA calculated that death rate among subjects receiving INH preventive therapy was 23.2 per 100,000 persons. Frequency of DILI from anti –TB medication is higher in Indian subjects compared to Western countries [15,42]

The number of cases of TB has increased dramatically in the past decade, especially in case of multi drug resistant strains. This has led to the use of combination therapy which consists of an initial induction phase of four drug viz, INH, rifampicin(RIF),

pyrazinamide (PZA), and ethambutol(ETH) for 2 months followed by a continuation phase of INH and rifampicin for 4 to 7 months. The first three drugs (INH, RIF, PZA) are bactericidal where as the last one (ETH) is bacteriostatic.Hepato-toxicities of the first three drugs are well documented. A meta analysis of ATT associated hepatotoxicity reported that the frequency of clinical hepatitis caused by INH, rifampicin, or both together was 0.6%, 1.1%, and 2.6%, respectively.

These spectrums of ATT hepatotoxicity is diverse, ranging from asymptomatic rise in aminotransferases in2.3% to 28% to acute liver failure (ALF) in approximately fewer than 0.01% of the individuals. There is a wide variation in incidence of ATT DILI in India in different studies as well as in the West (8%-30%) [43,44].In a recent study from Bombay Agal S et al showed the incidence to be 10.5% in their study population [18].Similar result was also published by Anand AC et al in another study [45].In an analysis of pooled data from four Indian studies ,the risk of clinical hepatitis due to anti tuberculosis drugs is estimated to be 11.5%.[20] .Bose PD,et al has reported the incidence of anti –TB DILI to be 18.8% in a recent study conducted in Delhi in patients with pulmonary TB[85].A meta analysis of studies from the West has shown it to be 4.28%(95% CI 3.38-5.28).The higher incidence of anti-TB DILI in Indian subjects may be as a result of genetic susceptibility, inherent peculiarity of drug metabolism ,under nutrition, or the presence of multiple risk factors like HBV/HIV infection. Also acute viral hepatitis is an important mimic of DILI in terms of clinical, biochemical and histological presentation. Sarda P et al has noted that acute viral hepatitis can complicate anti TB treatment in up to 14.7% of patients on ATT, in countries like India where hepatitis E virus infection is endemic [46].In a prospective study from a tertiary care hospital in North India, Singh J etal reported ATT –ALF in 9.7% of their study population of 72 patients and the mortality was 85.7%.[82].It has higher mortality than hepatitis due to hepatotropic viruses.

In other parts of the world also similar incidence is reported. A study conducted at a tertiary hospital in Iran has shown the incidence of anti-TB DILI to be 13% and mortality was about 13%.It occurred most frequently in the first 2 weeks of treatment and higher rate was noted in the elderly patients [47].A multi centre study conducted in Nepal identified that about 15% of DILI was due to ATT [48].In a nationwide survey of severe anti TB DILI in Japan ,the incidence was 0.50 to 0.59 % in three hospitals with good surveillance system and the overall incidence was 0.1% to 0.5% in the total study population. But 8 out of 29 patients (27.5%) died due to liver failure. Majority of these patients were on ATT for 2 months. Although they could not identify any specific risk factor for DILI, a higher bilirubin (>5mg%) was associated with poor outcome [49].In a prospective study of anti- TB DILI from Egypt(country which is endemic for liver diseases),the incidence was 15%.The majority of patients had DILI within one month of start of therapy. It was also noted that re introduction of pyrazinamide was associated with a fatal outcome [50].Nash KL, has reported a case of sub acute liver failure due to anti TB treatment which was successfully treated with orthotopic liver transplantation [51].Singh J etal, reported 4 cases of SAHF from North India[82].In another study from UK ,Wendon J et al has described successful orthotopic liver transplantation in 3of 4 patients of ALF due to anti-TB DILI referred to their centre[52].The prognosis in ATT ALF is extremely poor (less than 20% survival) and hence early referrel for liver transplantation is indicated.

In a recent study published from France, P.Ichai et al reports that ATT induced ALF contributed to2.8% of patients referred for liver transplant in the study period of 22 yrs [53].In another retrospective analysis of the data from the United Network for Organ Sharing Registry(UNOS),during the period of 1987-2006,0.07% of liver transplantation were for ALF due to anti-TB DILI.Majority of these cases were due to INH ,rest being caused by pyrazinamide and rifampicin [53].In a recent study from AIIMS ,ATT induced ALF constituted 70 of 1223 (5.7%) consecutive ALF patients admitted there over a period of 23

yrs [15].Most of the guidelines do not recommend routine monitoring of LFT in patients on ATT except in the setting of underlying CLD or other risk factors. In a prospective study conducted by S Agal etal ,they found that those patients who were on regular LFT monitoring while on ATT did not develop liver failure because ATT was promptly stopped when transaminits occurred .In those(control group) who were not on regular monitoring, many patients developed icteric hepatitis, of which a significant proportion developed liver failure requiring ICU care[18].

Pathogenesis of anti -TB DILI

Pathogenesis of anti-TB DILI is not well understood. Histopathological evidence resembles that of viral hepatitis-namely hepatocyte necrosis, ballooning degeneration, and inflammatory infiltrates. Although these can resemble dose related hepatotoxicity there is no direct relation between serum drug level and the degree of hepatocyte necrosis[54].Even though there are no sentinel features of reactive metabolite syndrome, the presence of eosionophils on liver biopsy as well as the recurrence of hepatotoxicity on re challenge indicates idiosyncratic hypersensitivity as a possible mechanism. Continuation of INH despite symptoms has been associated with a severe clinical course and fatal outcome. However compared with INH, DILI caused by Rifampicin occurs earlier .Histologically it is characterised by patchy hepatocyte necrosis with peri portal inflammation. It may occur as a part of systemic allergy response .Unconjugated hyperbilirubenemia can occur due competitive uptake with bilirubin. Even bridging necrosis, fibrosis and micro nodular cirrhosis have been reported in patients who died of rifampicin and pyrazinamide induced hepatotoxicity [41,55] The exact mechanism of DILI due to pyrazinamide is not known. It generally produces delayed hepatotoxicity, but this is not always the rule.INH is often associated with fulminent liver failure whereas pyrazinamide

often leads to sub acute hepatic failure. Significant transaminitis is reported in0.5% of patients on INH monotherapy, 1-2% of patients on Rifampicin prophylaxis. The risk associated with pyrazinamide in its current dosage is not known. But it was recently reported that it causes more hepatotoxicity than INH or rifampicin [41]

Metabolism and mechanisms of anti-TB DILI

Isoniazid

Isoniazid was first used in 1950s.It carries 20% risk of biochemical hepatitis although overt hepatitis is much lower [56]. Although both metabolic and immunologic factors are likely to be involved in DILI, investigation thus far has been focussed on the metabolic pathway of INH. The enzyme N-acetyltransferase (NAT) is responsible for the metabolism of INH to acetyl isoniazid which in turn is hydrolysed to acetyl hydrazine. The latter could be oxidised by CYP2E1 to from N-hydroxy-acetyl hydrazine, which further dehydrates to yield acetyl diazine. Acetyl diazien may itself be the toxic metabolite or may break down to reactive acetylonium ion ,acetyl radical, and ketene, which could bind covalently with hepatic macro molecules resulting in liver injury.NAT is also responsible for further acetylation of acetyl hydrazine to non toxic diacetyl hydrazine. Therefore, slow acetylation results not only in accumulation of the parent compound but also of monoacetyl hydrazine. Acetylation of acetyl hydrazine is further suppressed by INH itself. In addition, direct hydrolysis of INH without acetylation produces hydrazine that could cause liver injury. Liver biopsy usually shows necrosis with marked inflammatory activity which is the classic finding in idiosyncratic DILI [30].

Rifampicin

Rifampicin was introduced as first line anti TB treatment in 1960s.It undergoes desacetyaltion into desacetyl rifampin and on hydrolysis produces 3 –formyl rifampicin. Although rifampicin results in hepatocellular dysfunction early in the course, it can resolve spontaneously. There is no evidence of presence of any toxic metabolite and the mechanism of toxicity is largely unknown. The combined use of rifampicin with INH is more hepatotoxic since it is a potent inducer of CYP 450 enzyme system and also induces isoniazid hydrolase. Rifampicin causes transient elevation in hepatic enzymes usually in the first 8 weeks of therapy, but only in, 1% patients it presents as overt hepatitis [57].

Pyrazinamide (pyrazoic acid amide-PZA)

It is converted into pyrazinoic acid and the oxidised to 5(OH) pyrazinoic acid by xanthine oxidase. It is unknown that the drug itself or its metabolite produces toxicity. In animal models pyrazinamide has shown to inhibit different CYP 450 systems, but it is not documented in humans.PZA has a longer half life of about 10 hrs which is significantly increased in patients with underlying liver disease (up to 15 hrs).It can exhibit both dose dependent as well as idiosyncratic injury. Allopurinol along with PZA can be hepatotoxic because it can inhibit xanthine oxidase which is essential for the clearance of PZA. In studies done by Singh A et al , pyrazinamide even in lower doses is found to be hepatotoxic.

In general reactive metabolites formed during the biotransformation of drugs generate intra cellular oxidative stress which in turn induces mitochondrial membrane permeability transition.(MPT).The cellular consequence of MPT is loss of membrane potential that is required for ATP synthesis which ultimately leads to hepatocyte death mainly by necrosis[58].However drug metabolites simultaneously activate both injurious and protective pathways. The threshold for hepatocyte death can be modulated by intra cellular signal transduction and transcription factors for protective((NF E2 related factor 2-NRF2)

and injurious (c-Jun N-terminal Kinase-JNK)pathway [59].It is plausible that the balance between the activation of protective and injurious pathway may determine the clinical effects of reactive metabolite.NRF2 regulates glutathione synthetic and detoxification enzymes and NRF2 directed endogenous anti oxidant systems in the liver may dampen the injurious effect of reactive metabolites and lead to what is clinically recognised as “adaptation” .On the other hand if the oxidative stress is sufficiently high, it may overwhelm this anti oxidant system leading to serious DILI

In macrophages, it has been proposed that there exists a hierarchical response to oxidative stress [59].At low oxidant levels cells adapt to the stress by inducing a cyto-protective gene battery, comprising anti oxidant proteins, drug metabolising enzymes, heat shock proteins, and 26 s proteosome sub units in which the responsive genes each contain an antioxidant response element (ARE) in their promoters. The principle ARE containing anti oxidant genes that are induced by NRF2 include those for the glutamate cysteine lygase catalytic (GCLC) and modifier(GCLM) sub units, that catalyse the rate limiting step in glutathione biosynthesis as well as glutathione reductasse, thioredoxin,thioredexin reductase, peroxiredoxins,ferritin, metallothionine , and heme oxygenase 1.Recent investigations have demonstrated that activation of NK/NKT cells, major components of resident lymphocytes in the liver, play an important role in DILI. Intracellular stress of reactive metabolites activates both pro and anti inflammatory cascades which modulate the progression of liver injury into adaptation of serious DILI.

Risk Factors for anti-TB DILI

1) Demographic Factors -Advanced age (>60yrs), female sex, low BMI, low mid arm circumference, malnutrition are shown to increase the risk of ATT DILI [60-63].In one study it was found that anti-TB DILI in children was more common under age 5yrs,extra pulmonary TB and with the use of PZA. In a South Indian study TB DILI in children was noted in 16%-39% of TB meningitis patients. However no significant relation between BMI and risk of anti -TB DILI was noted in a study published by Anand AC etal[45].Also another study from India by Thiagu R et al did not find any statistically significant difference between males and females [64].Older patients have altered metabolism of drugs due to decreased levels of CYP 450 enzymes and the effect of con concomitant multiple drugs. There is also change in the hepatic blood flow as well as the volume of distribution. Females have a higher level and activity of CYP 3A and hence are at higher risk. Malnutrition results in poorer xenobiotic clearance and hence higher plasma levels.Singla R et al in a recent study has observed hypoalbuminemia (albumin<3.5g/gL) and malnutrition as predictors of anti-TB DILI[20].

2) HIV/AIDS- HIV infection increases the risk of DILI due to standard multidrug treatment. They have altered activities of oxidative pathways which might explain the cause.Also concurrent therapy with anti retroviral drugs results in over lapping toxicities and drug-drug interactions.. The incidence of DILI in anti retroviral treatment ranges from 2%-18%.It has been observed that HIV positive patients develop less hepatotoxicity compared to negative patients when rifampicin or pyrazinamide were given for treatment of latent tuberculosis[41].

3)Underlying liver disease.-Many studies have shown that Hepatitis B or C increase the risk of ATT DILI .One report from Taiwan has shown that ATT induced fulminent and sub acute hepatic failure were more common in the HBsAg carrier group. In general patients with underlying liver disease are at risk of DILI. However Lee BH et al have shown that ATT can be given safely as in the short course regimen in HBsAg positive and HBeAg negative in active carriers without any added risk, provided monthly LFT is done[65]Another study by Kaneko et al has shown that INH and rifampicin without PZA can be safely given in patients with chronic hepatitis[66].

4)Genetic risk factors-The genetic polymorphisms in different metabolising enzymes can alter the activity of enzymes and hence predispose one for DILI.T his may be because of different rate of formation of drug metabolites or adducts. Recently lots of data have come up on DILI and genetic risk factors. The proposed risk factors for anti-TB DILI are slow acetylators(without the NAT*4 allele),CYP P4502E1 homozygous wild type, Human Leukocyte Antigen DQ null mutations and the glutathione S –transferase homozygous null type(GSTM1).This can explain the different risk in various population[67-69].Hence regular monitoring of amnotransferase is important in patients receiving anti tuberculous treatment in case of slow acetylator [70].How ever in a study done by Singh J et al no significant difference was noted among slow or rapid acetylatiors in anti-TB DILI[71]. Severe DILI cases have shown to carry low or intermediate IL-10 producing haplotype and it was phenotypically expressed as low or normal eosinophils in peripheral blood[72].The role of genetic polymorphisms in Indian patients with anti-TB DILI i9s not well studied. Bose PD,et al has observed that NAT-2 slow acetylator genotypes to be significantly more in anti TB DILI patients than controls. They also observed a possible association between Dra1polymorphism of the CYP2E1 gene and risk of anti-TB DILI [85].

5) Intoxications- Alcohol can induce hepatic enzymes and hence is associated with a higher incidence of ATT DILI.

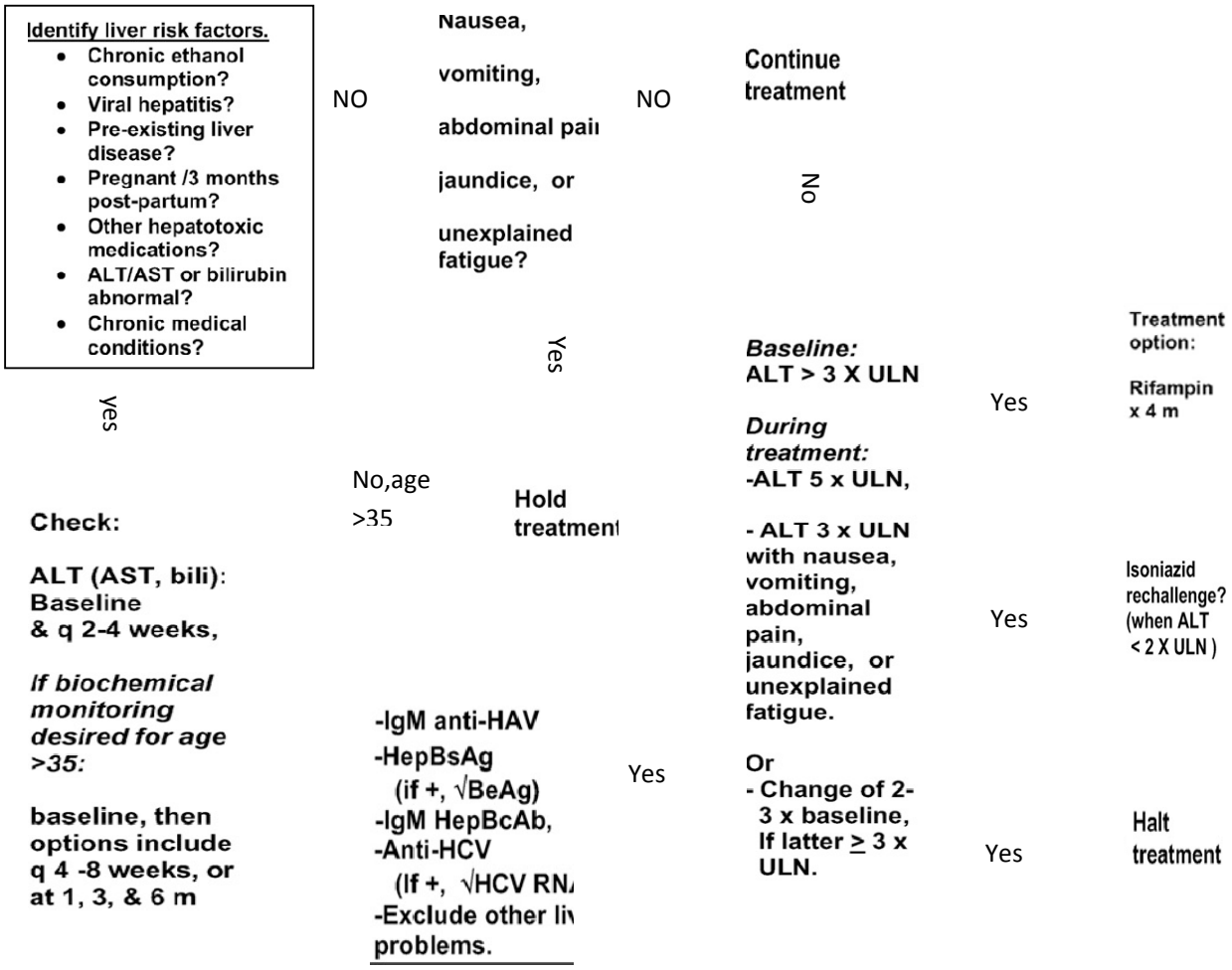
6) Dosing schedule- Several studies have shown that thrice –weekly regimen has less of hepatotoxicity than daily regimen [73].But recent studies have shown that it not true [74].In a study conducted at New Delhi Dhingra et al observed that the incidence of ATT DILI in DOTS therapy was significantly low –one out of 1195 patients [75] while a Hong Kong trial reported the rate to be 2%[76].

Management of anti-TB DILI

Several guidelines have been proposed by American Thoracic society (ATS), British Thoracic society(BTS),WHO and the Task Force for European respiratory Society[37 ,38].The first step is stopping the anti TB drugs when DILI is suspected. TB should be treated under the supervision of a qualified physician. They should seek medical attention when symptoms of hepatotoxicity develop viz, malaise, nausea, vomiting and jaundice. Regular monitoring of LFT is recommended in patients who have underlying chronic liver disease or increase in transaminsae prior to treatment [37].The treatment should be stopped if the transaminsases are elevated more than 5 times the upper limit of normal in the absence of symptoms, more than 3 times the upper limit in presence of symptoms or if bilirubin is more than 2 mg%. Asymptomatic transaminits can occur in up to 20 % of patients during anti TB treatment which can resolve spontaneously due to hepatic adaptation.ATS does not recommend baseline liver function test except in high risk patients where as the BTS and Task force recommend routine baseline LFT in all patients. Once TB treatment is stopped because of DILI, both ATS and BTS advocate for sequential reintroduction of drugs where as the Task Force advises all drugs simultaneously. A recent report published by Sharma SK et

al concluded that all the three different regimens were equally effective without higher risk although the arm which was started on full dose ATT had a mild increase in recurrence which was not statistically significant [77].The pre treatment albumin was the only statistically significant predictor of future recurrence of DILI.

In many developing countries the burden of TB is very high and routine monitoring by LFT cannot be recommended. In such situations the patient should be taught about the symptoms of hepatotoxicity and their presence should lead to prompt evaluation of LFT. Many patients have undergone successful liver transplantation after severe anti-TB DILI and they could be successfully restarted on anti TB treatment after transplantation [51,52]



Monitoring for hepatotoxicity during treatment of TB disease. *Adapted from ATS guidelines*.[37]

Future Directions

The mechanisms of TB DILI are still largely unknown. Further studies on genetic polymorphisms of enzymes involved in drug metabolism is required to identify patients who are at risk of ATT DILI.Truly 'predictive biomarkers' can reliably identify patients, in whom exposure to a specific drug can be avoided. As the balance of injurious vs anti oxidant pathways determine the evolution of mild injury secondary to a reactive metabolite into an 'adaptation' or serious DILI,many studies are aimed to develop an optimal combination of products of oxidative stress, cellular response and cytokines that modulate the inflammatory response as biomarkers that would help to distinguish adaptation from serious DILI. One such approach is metabolomics which focuses on broad identification and analysis of multiple metabolites simultaneously. Recent human clinical trials of drugs, have shown that the metabonomics of bio-fluids collected before and immediately after dosing can identify individual patients who are likely to develop DILI. It is said to be complimentary to or potentially superior to genetic testing for identifying risk in DILI. Another area of research is Transcriptomics which is aimed at identifying liver derived mRNAs in the cell free plasma in patients with DILI. Proteonomics involves identifying protein biomarkers in patients with DILI (e.g,Cytokines).Another test commercially available and used in Japan is the lymphocyte transformation test which involves culturing of the pateint's lymphocytes in the presence of suspected drug.In positive test there is proliferation of lymphocytes which can be measured in several ways. DILIN network is doing ancilliary study to critically assess the value of this test.

Materials and methods

The present study is a case control study which is partly retrospective and partly prospective. Consecutive patients with anti tuberculous treatment induced liver failure admitted in the department of Clinical Gastroenterology and Hepatology, Christian medical college, Vellore from January2006 to January 2011 were studied. Those patients who attended the Liver clinic or Medicine III OPD with asymptomatic or symptomatic anti tuberculous treatment induced hepatitis from January 2009 to January 2011 were taken as the controls. Consent to include in the study and analysis was taken from the patient or nearest relative in all the prospectively studied patients. The study protocol was approved by the Institutional review board.

Inclusion Criteria

Cases- All patients of anti-TB DILI (ie, those who are on one or more of the first line hepatotoxic anti tuberculous drugs-INH, Rifampicin or Pyrazinamide) with liver failure (acute liver failure and sub acute hepatic failure). Causality assessment was made using the RUCAM score (Russel Uclaf Causality Assessment Model).Those with a score of >5 were included.

Controls-Patients on anti tuberculous treatment that includes any regimen containing Isoniazid, Rifampicin or Pyrazinamide who have symptomatic or asymptomatic transamintis without any evidence of liver failure.

Exclusion criteria

- All cases of TB DILI with RUCAM score less than ≤5.
- Patients on non hepatotoxic ATT regimen.
- Patients with acute viral hepatitis while on ATT.
- Patients who failed to give consent.

Study variables

Acute Liver Failure (ALF)-was defined as presence of jaundice complicated by encephalopathy within four weeks of the onset of jaundice in the absence of pre existing liver disease.[78]

Sub acute hepatic failure (SAHF)- is a distinct condition defined by the persistence of jaundice complicated by hepatic decompensation in the form of ascites and or encephalopathy from fifth to twenty fourth week in the absence of pre-existing chronic liver disease.[78]

Acute on chronic liver failure (ACLF)- is defined as the acute hepatic insult manifested as jaundice and coagulopathy complicated within 4 weeks by ascites and or encephalopathy in a patient having diagnosed or undiagnosed chronic liver disease.

ATT induced hepatitis (AIH)- was defined as elevation of serum transaminase (alanine amino transferase-ALT and/or aspartate amino transferase-AST) more than 2 times the upper limit of normal (ULN) in the presence of symptoms or more than 5 times the ULN in the absence of symptoms. The symptoms suggestive of hepatitis are nausea, vomiting, anorexia, malaise, right upper quadrant abdominal discomfort, jaundice, and skin rash.

Grading of encephalopathy [80]

Grade 1: Personality changes, attention deficits, irritability, depressed state

Grade 2: Changes in sleep-wake cycle, lethargy, mood and behavioural changes, cognitive dysfunction

Grade 3: Altered level of consciousness (somnolence), confusion, disorientation, and amnesia

Grade 4: Deep unconscious state, with absence of response to painful stimuli.

Renal failure was diagnosed if patients developed decreased urine output (<400 mL in 24 hours), with serum creatinine greater than 1.4 mg/dL despite hydration, objectively assessed by central venous pressure of 10 cm saline or more.

Prognostic factors analysed in the present study were grade of encephalopathy ,S.Bilirubin, prothrombin time, renal failure (creatinine more than 1.4mg%) ,elevation in liver enzymes, ascites,spontaneous bacterial peritonitis, age >35yrs, sex, duration of ATT, continuation of ATT despite symptoms, alcohol consumption, underlying chronic liver disease or chronic hepatitis, past history of drug induced liver injury.

Outcome measured was survival or death/discharge against medical advice.

Management protocol

All patients with liver failure (ALF, SAHF or ACLF) were admitted to the High Dependency Unit (HDU) or the medical intensive care unit for management and monitoring. History was obtained from the patient or the nearest relative. For those patients who were admitted before January 2009, retrospective analysis was done from the case records in terms of clinical presentation, laboratory vales, management and outcome.

A uniform management protocol was present in the hospital for all patients. Those who had encephalopathy were on regular monitoring, antibiotics(after taking blood cultures) and antifungal prophylaxis (in case of ALF),stress ulcer prophylaxis, anti coma measures(mannitol or lactulose),blood sugar monitoring, and elective ventillatory support in case of grade IV encephalopathy. Antibiotics were continued until clinical improvement or resolution of any infection.Hemodialysis was used whenever indicated. All hepatotoxic anti tuberculous drugs were stopped and non hepatotoxic regimen using ethambutol, quinolones were used whenever indicated. Aminoglycosides were routinely not used until liver failure resolved. Adverse events such as renal failure, spontaneous bacterial peritonitis, gastro intestinal bleed, and death were recorded. Liver biopsy was performed (via Transjugular route) under FFP cover whenever diagnostic dilemma/persistently abnormal LFT existed. Although liver transplantation was done in this hospital, none underwent the same, due to scarcity of cadaveric donors.

Blood investigation done included LFT at base line including bilirubin, AST, ALT, albumin, alkaline phophatase, gamma glutamyl transpeptidase, prothrombin time, activated partial thromboplastin time, renal function test, and ascitic fluid analysis (including protein, albumin, cell count and culture). Ultrasonography of abdomen or CECT abdomen was carried out in all patients to rule out evidence of chronic liver disease, biliary obstruction and ascites. Appropriate tests for autoimmune hepatitis (ANA,Anti LKM antibody) and for Wilson's disease (s.ceruloplasmin, 24 hour urinary copper) were done in the liver failure group when ever indicated.

Markers of acute viral hepatitis were done in all suspected patients of anti-TB DILI. These include IgM (Immunoglobulin)anti-hepatitis A virus((ET-HA-IGMK PLUS,Diasorin,S.p.A,Saluggia,Italy),IgMantihepatitiaE(MPDiagnostics,St.Ingbert,Germany), IgM ant- hepatitis B core antigen and /or hepatitis B surface antigen(ETI-MAK-4 Diasorin S.p.A,Saluggia,Italy),and anti hepatitis C virus antibodies(AXSYM HCV Version 3,Abbot,Wesbaden Germany).Serological testing for HIV1 and 2 were also done in all patients of liver failure and majority of patients with hepatitis.(AXSYM HIVAg/AbCombo,Abbot,Wesbaden,Germany). Prothrombin time prolongation over control was done once in 2 days in every patient.

Statistical Analysis

Normally distributed continuous variables were expressed as mean(SD),and those with skewed deviation were expressed as median (Range).For analysing the cases and controls as well as difference between survivors and non survivors, Fisher's exact test was used for continuous variables and Student's t-test was used for discrete variables. Factors with a predictive value of <0.1 on univariate analysis were taken for binary logistic regression analysis and a p value of 0.05 was considered as significant. In patients with liver failure, we analysed the factors predicting death by Student's t-test. We dichotomised the variables by drawing a ROC curve and found cut-off and odds ratio for predicting death. Odds ratio with 95% confidence interval for each variable is reported. Data were analysed using SPSS software version 17.0(SPSS, Chicago, IL) and STATA (version 9.2).

Results

A total of Sixty seven patients who developed features suggestive of drug induced liver injury while on anti tuberculous drugs were identified during the study period. Four patients were excluded because they did not met the inclusion criteria-3 patients were IgM anti-HEV positive and one was IgM anti HBc positive. Hence 63 patients were included in the study.

Of these, 35(55.5%) patients had features of liver failure in the form of either ALF (n=9), SAHF (n=19) or ACLF(n=7).ATT induced hepatitis without liver failure was noted in 28 patients(44.4%).The spectrum of the disease in the present study is depicted in Figure 1.Two patients in the liver failure group had underlying chronic HBV infection and one had chronic HCV infection. Majority of these patients were on empiric anti tuberculous treatment (n=28,44%),pulmonary TB was present in 17(26.9%),and extra pulmonary TB in 18(28.5%) patients.(Fig.2) .Extra pulmonary TB included intestinal TB,TB meningitis, TB spine and Tuberculous pericarditis..Majority of patients on empiric ATT were initiated by general physicians from elsewhere without proper evaluation and these patients came to us for subsequent evaluation following anti-TB DILI.

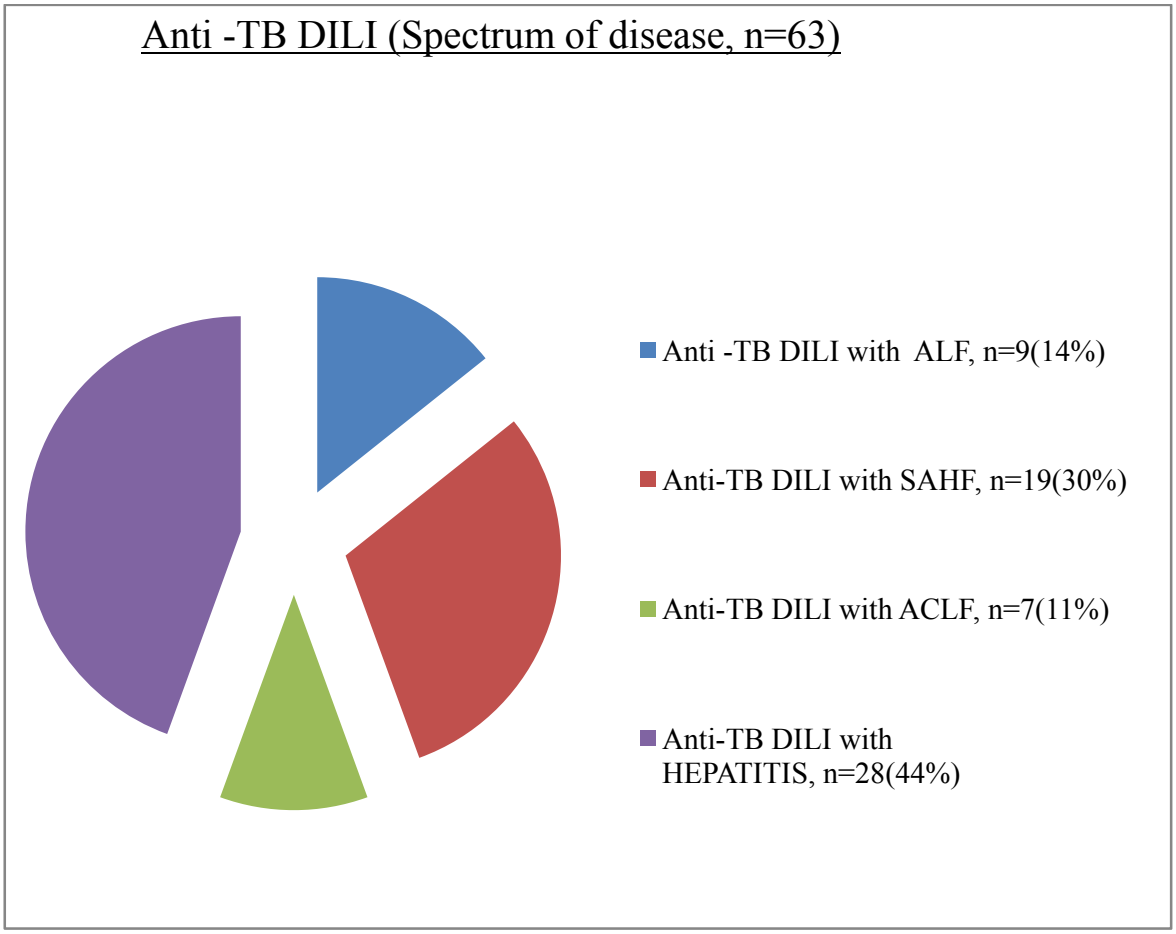


Figure 1.Shows the spectrum of presentation in the present study of 63 patients with anti-TB DILI.

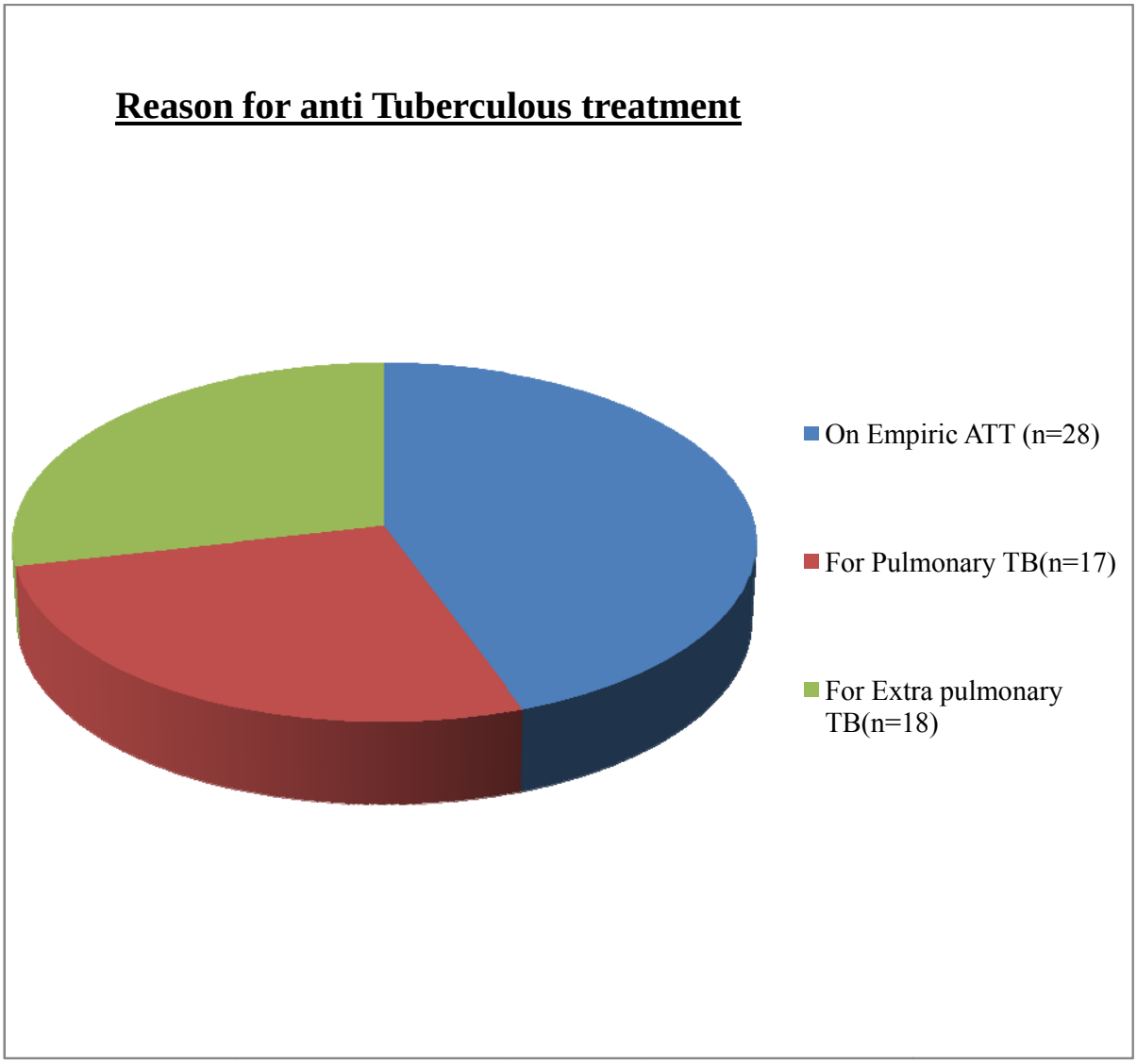


Figure 2.Indication for initiating anti Tuberculous treatment in the present study (n=63)

Clinical profile, laboratory parameters and complications in ALF, SAHF, ACLF and acute Hepatitis groups

The mean age (yrs) and range in different groups namely, ALF, SAHF, ACLF and Hepatitis were33.78±19.73 (17-73), 40.47±13.67 (9-58), 51±11.44 (35-65) and35.50±17.10 (5-66) respectively. Majority of patients with anti-TB DILI were above 35 yrs (n=35,55.5%).Females formed the majority of patients in the ALF(n=5,55.5%) and ACLF(n=5,71.4%) groups, whereas males were more common in the SAHF(n=12,63.1%) and the acute Hepatitis(n=15,55.35%) groups.

Past history of anti -TB DILI was present in 2 patients and they presented with ALF. All the patients (n=63) were on hepatotoxic ATT and the duration of ATT prior to presentation varied from 1 week to 52 weeks. Majority of patients in the ALF, SAHF, ACLF and acute hepatitis groups were on empiric ATT without any definitive etiological diagnosis. Significant alcohol intake was present only in 4 out of 63 patients. Underlying diabetes was present in 12 of 63(19%) patients. Three patients had underlying chronic hepatitis (2 - chronic HBV and 1- HCV infection) and seven had features of chronic liver disease on imaging and /or liver biopsy. Majority of patients who developed live failure were continuing ATT in spite of symptoms -5(55.5%) in ALF, 14(73.6%) in SAHF and 6(66.6%) in ACLF groups, whereas in the Hepatitis group only 6(21.4%) continued the drug in spite of symptoms or deranged LFT. Clinical profile and base line characteristics of different groups are represented in table 1.

Majority of patients presented with jaundice, vomiting, and anorexia which were common to all the groups. Hypersensitivity reactions in the form of skin rash/urticaria was noted in 8/63 patients. Overall 10 patients in the acute hepatitis group had asymptomatic LFT derangement. Ascites was present in 3(33.3%), 19(100%), 6(85.7%), and 2(7%) in ALF, SAHF, ACLFand the hepatitis groups respectively. 2 patients in the hepatitis group had abdominal tuberculosis and both had exudative ascites with lymphocyte predominance. Encephalopathy was the defining symptom in the ALF group (100%) and was present in 9(47.3%), 5(71.4%) in the SAHF and ACLF groups respectively. The most common complication noted was acute renal failure which was present in 9(25.7%) patients in the liver failure group followed by spontaneous bacterial peritonitis (n=8, 22.8%).The overall mortality in the anti-TB liver failure group was 20 out of 35(57.1%).The mortality in different subgroups were 8(88.9%), 8(42.1%), and 4(57.1%),for ALF,SAHF and ACLF respectively. One patient in the acute hepatitis group died because of underlying lymphoma. The clinical presentations and complications are depicted in table2.

The various laboratory parameters in the different groups with anti-TB DILI is represented in table3.The calculated MELD score for the liver failure group is also mentioned. In the liver failure group 9 patients underwent liver biopsy (post-mortem or elective trans-jugular liver biopsy under FFP cover in cases of diagnostic dilemma.).None of the biopsy showed any specific changes. Only 1 patient in the ALF group had liver biopsy and it showed extensive macro-vesicular steatosis with mild perivenular hepatocyte cholestasis and erythrophgocytosis. Seven patients in the SAHF group underwent TJLB since there was a suspicion of underlying chronic liver disease (auto immune hepatitis/overlap syndrome, Wilson’s disease, atypical copper associated liver disease).The most common finding was extensive bridging necrosis with early fibrosis and marked ductular and hepatocyte cholestasis.

Clinical profile and baseline characteristics of anti-TB DILI

Variables	Liver Failure (n=35)			A/c Hepatitis (n=28)
	ALF(n=9)	SAHF(n=19)	ACLF(n=7)	
Age(yrs),mean±SD Range	33.78±19.73, (17-73)	40.47±13.67(9-58)	51±11.44, (35-65)	35.50±17.10, (5-66)
Females, n (%)	5(55.5%)	7(36.8%)	5(71.4%)	13(46.4%)
Duration of ATT(wks)	8(2-16)	7(1-52)	18(8-40)	4(1-24)
Past H/O DILI	2	0	0	0
Reason for ATT, n (%) Pulmonary Extra pulmonary Empiric	 5(55.5%) 0 4(44.4%)	 2(10.5%) 7(36.8%) 10(52.6%)	 3(42.8%) 1(14.2%) 3(42.8%)	 7(25%) 10(35.7%) 11(39.2%)
Alcohol intake	1	1	1	1
Diabetes Mellitus	1	4	3	4
Underlying CLD/CH	0	3	7	0
Continuation of ATT despite symptoms	5(55.5%)	14(73.65)	6(66.6%)	6(21.4%)

Table1.ALF-acute liver failure, SAHF-sub acute hepatic failure, ACLF-acute on chronic liver failure .A/c –acute, CLD-chronic liver disease, and CH-chronic hepatitis.DILI-drug induced liver injury.

Clinical presentation and complications of patients with anti-TB DILI

Variables	Liver Failure(n=35)			A/cHepatitis(n=28)
	ALF(n=9)	SAHF(n=19)	ACLF(n=7)	
Jaundice (n,%)	9(100)	19(100)	6(85.7%)	17(60.7%)
Vomiting	6(66.6%)	11(57.8%)	4(66.6%)	18(64.2%)
Rash	2(22.2%)	1(5.2%)	1(14.2%)	4(14.2%)
Ascites	3(33.3%)	19(100%)	6(85.7%)	2(7%)
Encephalopathy	9(100%)	9(47.3%)	5(71.4%)	0
SBP	1(1.1%)	4(21%)	3(42.8%)	0
Renal Failure	4(44.4%)	3(15.7%)	2(28.5%)	0
Mortality	8(88.9%)	8(42.1%)	4(57.1%)	1(3.5%)

Table2.ALF-acute liver failure, SAHF-sub acute hepatic failure, ACLF-acute on chronic liver failure. A/c-acute, CLD-chronic liver disease, CH-chronic hepatitis.DILI-drug induced liver injury. SBP-Spontaneous bacterial peritonitis.

Laboratory parameters in patients with anti-TB DILI

Variables	Liver failure (n=35)			A/cHepatitis(n=28)
	ALF(n=9)	SAHF(n=19)	ACLF(n=7)	
T.Bilirubin(mg/dl)	16.5(4.8-32.8)	19(3.4-32)	22.2(1.4-31.5)	2.9(0.4-14)
ALT(IU/L)	550(91-946)	77(24-386)	150(58-309)	129(45-564)
AST(IU/L)	461(91-1116)	114(52-349)	139(55-599)	105(19-551)
Alk.Phosphatase(IU/L)	169(134-454)	191(59-688)	131(92-352)	113(58-593)
S.Albumin(g/dl)	2.55±0.54	2.22±0.42	2.55±0.47	3.35±0.84
PT(seconds)	97.35±28.87	21.98±5.86	33.57±9.43	13.1±2.486
APTT(seconds)	124.57±54.94	43.72±8.86	59.94±23.15	33.84±5.93
MELD score	42(27-57)	23(15-46)	30(8-42)	

Table3.ALT-Alanine aminotransferase.AST-Aspartate amino transferase, Alk.Phosphtase-Alkaline phosphatase, PT-Prothrombin time, APTT-Activated partial thromboplastin time. MELD score-Model end stage liver disease.

Risk factors for ATT induced liver failure (compared to ATT induced acute hepatitis.)-Clinical parameters

Apart from assessing the clinical profile, the present study also looked into the risk factors that determine the development of liver failure (compared to acute hepatitis) following anti-TB DILI. Patients who have compensated or decompensated chronic liver disease already have poor hepatic reserve and synthetic function, and so they are at risk of anti TB DILI. Hence the acute on chronic liver failure group (ACLF) was excluded for this analysis.

The clinical parameters that determined the liver failure in anti TB-DILI were duration of ATT for more than 5 weeks(p=0.01),continuation of ATT despite symptoms(p=<0.001) and the presence of icterus(p=0.01).The laboratory parameters that were significantly different between the two groups include high serum bilirubin (p=<0.001),low albumin(p=<0.001),prolonged prothrombin time(p=0.002) and prolonged partial thromboplastin time(p<0.001).There was no significant difference between the two groups in terms of rise in liver enzyme or pattern of LFT(hepatocellular, cholestatic or mixed).The two groups are compared in tables 4&5.On Multivariate analysis with logistic regression the factors that predicted liver failure following anti-TB DILI were 1)continuation of drugs despite symptoms (p =0.003,odds ratio 7.74(95%CI -2.32-25.74) and 2)duration of ATT for more than 5 weeks(p=0.031,odds ratio 4.88(95% CI-1.351-15.79).

Risk factors for ATT induced liver failure (compared to ATT induced hepatitis.)-Clinical parameters

Variable	Liver failure(n=28) ALF and SAHF	Hepatitis(n=28)	P value
Age(yrs)	38.32±15.14	35.50±15.10	0.52
Females(n,%)	12(42.8%)	13(46.4%)	1
Past h/o DILI(n,%)	2(7.1%)	0	1
Duration of ATT more than 5 Wks (n,%)	16(57.1%)	6(21.4%)	0.01
Continuation of ATT despite symptoms (n,%)	19(67.8%)	6(21.4%)	<0.001
Alcohol(n)	2	1	1
Diabetes (n)	5	4	1
Underlying Chronic hepatitis (n)	3	0	0.23
Jaundice (n)	28	17	0.01
Vomiting	17	18	1

Table 4. Liver failure includes ALF and SAHF (Acute on chronic liver disease is excluded).

Risk factors for ATT induced liver failure (compared to ATT induced hepatitis.)-Laboratory parameters at admission

Variables	Liver Failure (n=28) ALF and SAHF	Hepatitis (n=28)	P value
Bilirubin	18.42±8.87	3.85±3.51	<0.001
ALT	101(24-946)	129(45-564)	0.45
AST	148(52-1116)	105(19-551)	0.1
Alkaline phosphatase	188(59-688)	113(58-594)	0.1
LFT pattern- Hepatitic/cholestatic/mixed	18/2/8	24/0/4	0.12
Albumin	2.33±0.48	3.35±0.85	<0.001
Prothrombin time	25.25(13.9-120)	13.5(9.5-18.6)	0.002
Partial thromboplastin time	46.85(31-180)	32.3(23.8-48.9)	<0.001

Table 5. Liver failure includes ALF and SAHF (Acute on chronic liver disease is excluded).

Prognostic factors in anti-TB DILI

On univariate analysis, the clinical predictors of poor prognosis were- past history of anti -TB DILI (p=0.03),duration of ATT more than 5 weeks(p=0.004),continuation of ATT despite symptoms(p=0.04)and the presence of underlying CLD or chronic hepatitis(p=0.05).The presence of jaundice (p=0.001),hepatic encephalopathy(p<0.001) and ascites (p=0.03) at admission also predicted poor prognosis. The laboratory variables that determined poor outcome were high serum bilirubin (p<0.001), low albumin (p=0.003), prolonged prothrombin time(p=0.001) and partial thromboplastin time(p=0.001) as well as the presence of renal failure(p<0.001).The variables analysed in prognostic factors in anti - TB DILI are represented in tables 6,7.

Prognostic Factors in anti -TB DILI -Clinical parameters.

Variables	Survivors(n=42)	Non survivors(n=21)	p value
Age(yrs)	38.93±16.82	37.57±15.16	0.76
Females (n, %)	17(40.4%)	13(61.09%)	0.10
Past h/o DILI (n,%)	0	2	0.03
Duration of ATT more than 5 Wks (n)	14	15	0.004
Continuation of ATT despite symptoms (n,%)	17	14	0.04
Alcohol(n)	2	2	0.4
Diabetes (n)	8	4	1
Underlying CLD/ Chronic hepatitis (n)	4	6	0.05
Jaundice (n)	30	21	0.001
Vomiting	26	13	1
Rash	5	3	0.7
Hepatic encephalopathy	5	18	<0.001
Ascites	16	14	0.03

Table 6

Prognostic factors in anti- TB DILI-Laboratory variables.

Variables	Survivors(n=42)	Non survivors(n=21)	P value
Bilirubin	4.6(0.4-26.8)	22.2(3.9-32.8)	<0.001
ALT	111.5(24-946)	141(54-920)	0.27
AST	114.5(19-620)	257(73-1116)	0.08
LFT pattern- Hepatitic/cholestatic/mixed	34/1/7	13/2/6	0.21
Albumin	2.99±0.88	2.44±0.52	0.003
Prothrombin time	14.45(9.5-49)	40(30-120)	0.001
Partial thromboplastin time	36.5(23.8-59.5)	61.3(31-180)	0.001
Complications Renal failure	1	8	<0.001
SBP	4	4	0.29

Table 7.ALT,-alanine amino transferase, AST-aspartate amino transferase,SBP-Spontaneous bacterial peritonitis

Predictors of outcome in anti-TB DILI with liver failure (ALF, SAHF&ACLF)

In the present study a total of 35 patients presented with features of liver failure (ie., ALF, SAHF& ACLF).Of these 35 ,20 patients succumbed to the illness leading to an overall mortality of 57.1%.In the individual groups the mortality was 8(88.9%),8(42.1%) and 4(57.1%) for ALF,SAHF and ACLF respectively. The outcome in different groups is depicted in figure 3 .Subgroup analysis was done to identify the factors that predicted the outcome-survival or death. The factors found to be significant on univariate analysis were age (survivors 46.8±14.46 vs. non survivors 36.4±14.5, p =0.04), serum bilirubin (survivors 13.48±8.1vs non survivors 22.9±8.36, p=0.002),prothrombin time(survivors 23.46±8.9 vs non survivors58.7±40.8,p=0.001),and MELD score(survivors 22±6 vs non survivors 36±10,p<0.001).

All continuous variables were dichotomised by the construction of receiver operating characteristics curves for identifying cut off values between the survivors and the non survivors. The curve was constructed using a value of serum bilirubin, prothrombin time and MELD score for each patient as independent variables and mortality as the outcome. The area under the curve was 0.787, 0.833 and 0.870 for serum bilirubin, prothrombin time and MELD score respectively. A cut off of s.bilirubin at 13 mg/dL was found to be 95% sensitive and 56% specific for predicting mortality. Prothrombin time greater than 23.3 sec was 85% sensitive and 76% specific for predicting mortality where as MELD score more than 23 was 90% sensitive and 60% specific for predicting mortality. The odds ratio for s.bilirubin >13mg/dL was 21.71(95% CI,2.28-206.48),prothrombin time >23.3sec was 11.33(95% CI,2.21-57.87) and MELD score >23 was 21.71(95% CI ,2.28-206.48).The median (range)

time of death from the day of hospitalisation in ALF group was 5(1-8days),SAHF was 18(4-41 days) and the ACLF was 5(4-18 days).

Outcome in anti-TB DILI with liver failure(ALF,SAHF& ACLF) and Hepatitis

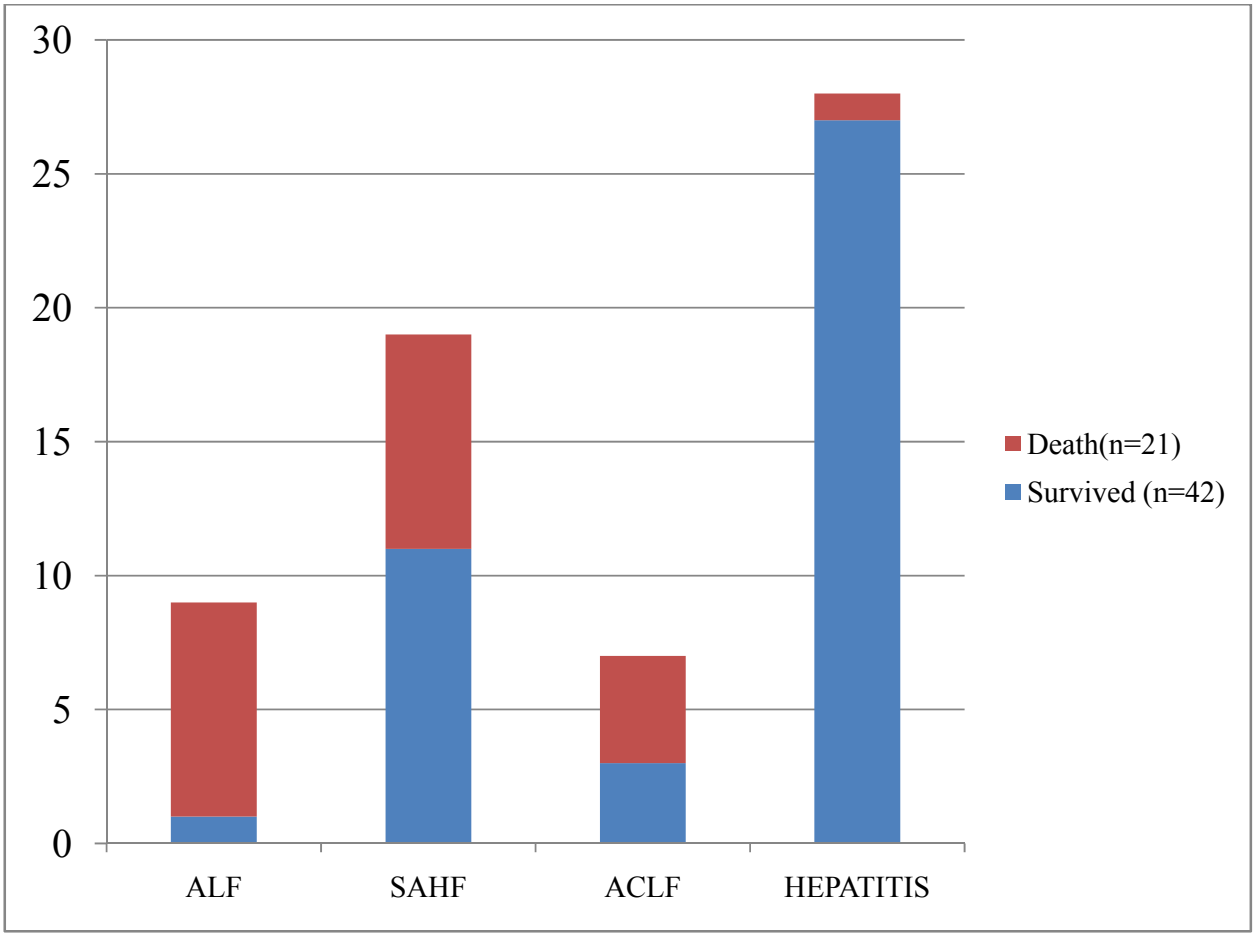


Figure3. .ALF-acute liver failure, SAHF-subacute hepatic failue,ACLF-acute on chronic liver

Determinants of outcome in anti-TB Liver failure(ALF,SAHF,ACLF)

Variable	Survivors(n=15)	Non survivors(n=20)	P value
Age	46.8±14.46	36.4±14.5	0.04
Bilirubin	13.48±8.1	22.9±8.36	0.002
Prothrombin	23.46±8.9	58.7±40.8	0.001
MELD score	22±6	36±10	<0.001

Table 8MELD- Model end stage liver disease score

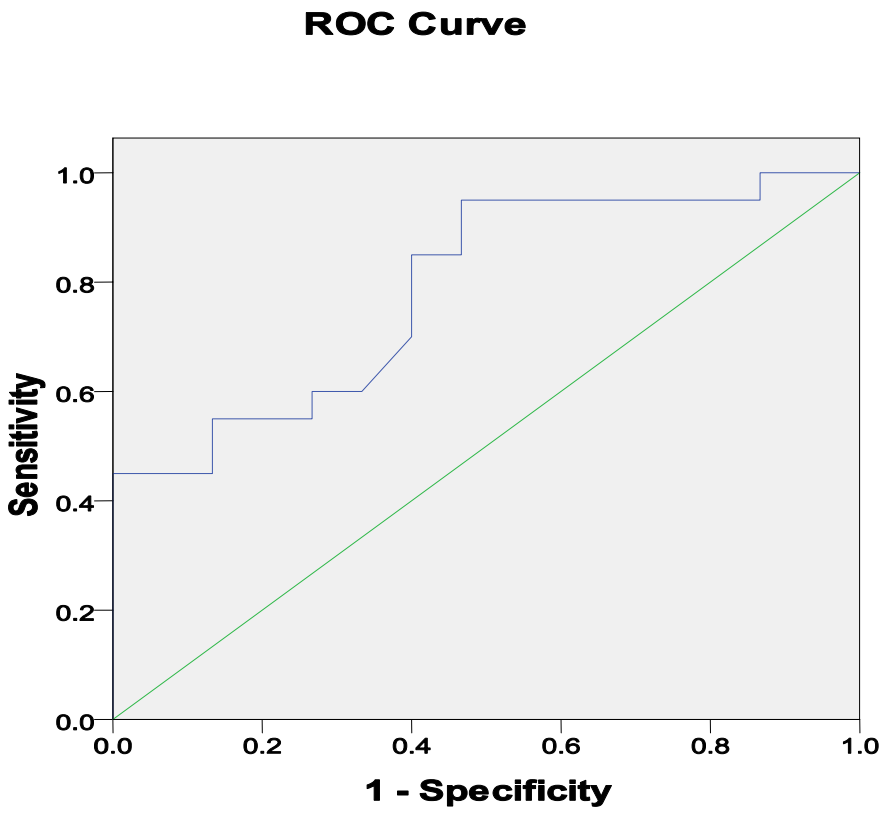


Fig 4 Receiver operating charecteristic curve of serum bilirubin and mortality.Area under the curve is 0.787

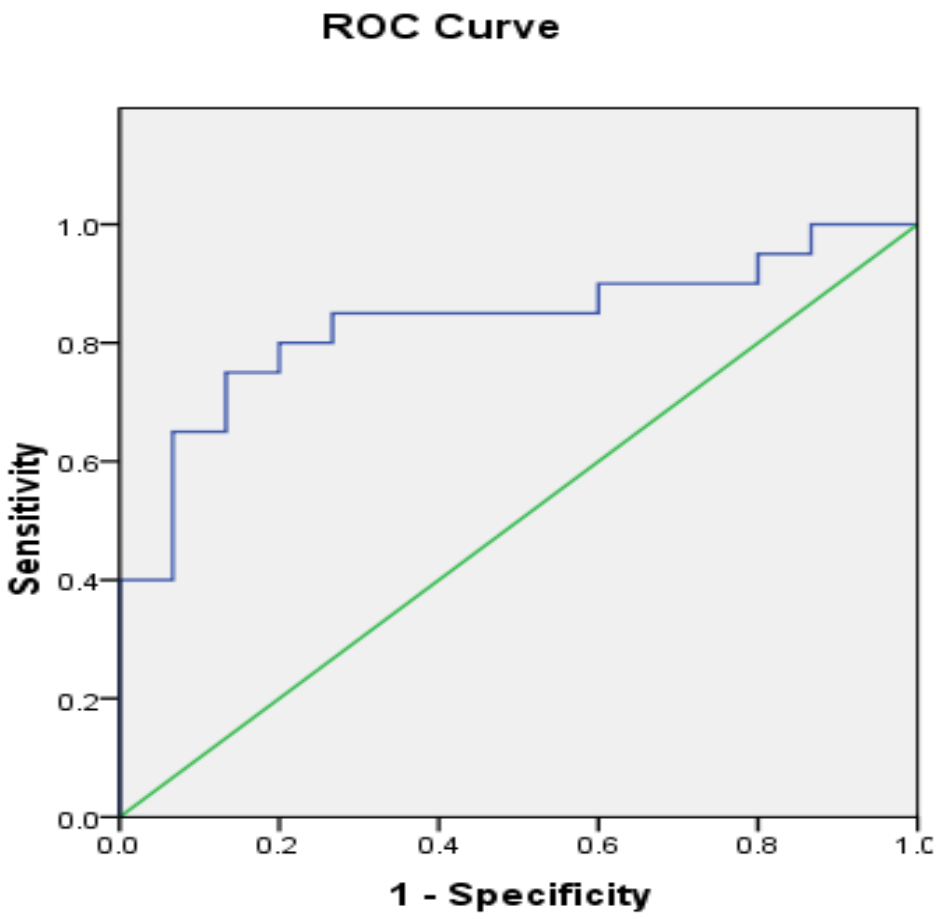


Fig 5 Receiver operating charecteristic curve of Prothrombin time and mortality. Area under the curve is 0.833

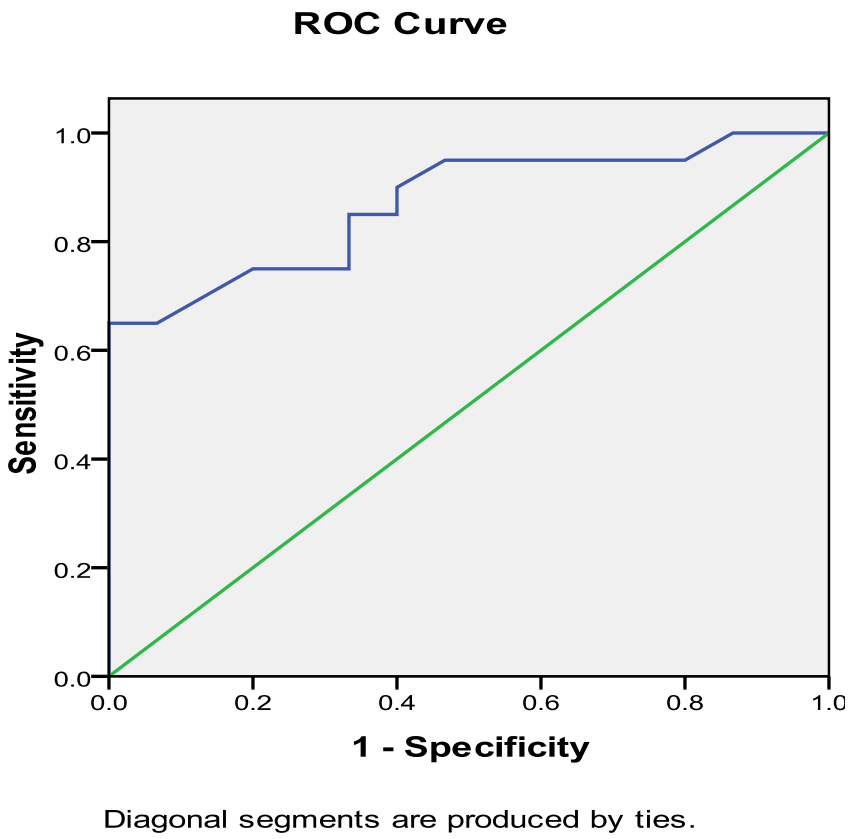


Fig 6 Receiver operating charecteristic curve of MELD score and mortality. Area under the curve is 0.870

Discussion

The development of anti-TB DILI during chemotherapy is the most common reason for discontinuation of therapy and it results in inadequate as well as increased duration of therapy. A combination of INH, rifampicin and pyrazinamide produces more DILI than any of these drugs given alone. There is a wide variation in the incidence of anti- TB DILI in India in different studies as well as in the West (3%-30%) [43,44,81]. In an analysis of pooled data from four Indian studies ,the risk of clinical hepatitis due to anti tuberculosis drugs is estimated to be 11.5%.[20]].In a prospective study from a tertiary care hospital in North India, Singh J etal reported ATT –ALF in 9.7% of their study population of 72 patients and the mortality was 85.7% [82]. In a recent study from AIIMS, ATT induced ALF constituted 70 of 1223 (5.7%) consecutive ALF patients admitted there over a period of 23 yrs [15] with mortality of 67.1%.The present study has looked into the burden of ATT induced liver failure compared with ATT induced hepatitis and its clinical significance. It is estimated that a patient taking ATT has a 0.01% risk of developing ALF [37]. However there are no prospective studies which have looked into the incidence of SAHF or ACLF following anti-TB DILI. Although the proportion of ALF patients may appear low, the absolute value will be very high because approximately 3 million people in India are suffering from tuberculosis and are on ATT.

Several studies have looked into the risk factors for developing anti-TB DILI.It is still not clear why some patients develop DILI whereas some do not. It also not known who develop liver failure following anti-TB DILI , while the majority develop hepatic

adaptation. In the present study a total of 63 patients who developed different spectrum of anti- TB DILI were analysed. Here we used RUCAM score (the Roussel Uclaf Causality Assessment Model) for assessing the causality in anti-TB DILI.A score of >5(probable DILI) was taken as significant in defining DILI.

In the liver failure group, 9 patients presented with ALF. Although many studies have not found any significant gender difference in DILI, it has been observed that fulminent liver failure is more common in females and hence worse outcome including mortality[27].In the present study ALF was more common in females(5of 9,55.5%) and none survived.8 out of 9 patients with ALF died and overall mortality was 88.9%. There are only 2 published case reports of SAHF due to anti-TB DILI available in literature.[51,82].The current study has the largest data on SAHF due to anti-TB DILI(n=19).In SAHF group majority of patients were males(n=12,63.15%) and mortality was less compared to ALF(n=8,42.1%).They had a prolonged hospital stay before they discharged/died. Pyrazinamide is often associated with sub acute hepatic injury [41].All the patients in the SAHF group in the present study were on Pyrazinamide along with the other first line anti tuberculous drugs. Although it is known that underlying chronic liver disease is a risk factor for DILI, there is scarcity of published literature in ACLF due to anti-TB DILI. 7 patients in the present study had ACLF ,the acute insult being anti-TB DILI. Of these 6 patients were not known to have CLD prior to starting ATT. Majority were females (n=5,71.4%) and mortality in this group was 57.1%(n=4).

In the liver failure group majority of patients were on empiric ATT (n=17,48.5%), and the rest were on ATT for Pulmonary(n=10,28.5%) and extra pulmonary TB(n=8,22.5%).Most of the patients on empiric ATT were initiated by general practitioners

without proper evaluation, which could have been avoided. The most common clinical presentations in liver failure group was jaundice (97.1%), vomiting (60%), ascites (80%) and encephalopathy (65.7%).

The reported incidence of anti TB DILI due to DOTS regimen is less. However Singla etal has reported the incidence to be around 14.3% in their study group which is as comparable with the daily regimen of ATT [20].But reports on liver failure due to DOTS is meagre. In the current study we came across 4 patients with liver failure who were on DOTS regimen. Hence it can be assumed that DOTS regimen may not decrease the incidence of mild or serious DILI due to anti TB drugs. In India, where acute HEV infection is endemic, viral hepatitis is always a confounder in ant-TB DILI. Sharma S.K has reported that 10-15% of suspected anti-TB DILI can have acute viral hepatitis [83] as a confounder. In the present study 3 patients had acute HEV infection and one had acute HBV infection. All were excluded as it was a part of exclusion criteria. Studies have shown that viral hepatitis will have larger rise in aminotrasferases and take longer time for normalisation of LFT as compared to anti-TB DILI and these patients can be safely restarted on regular ATT after normalisation of LFT.Hence routine screening of all patients with suspected anti-TB DILI for viral markers is recommended.

Several studies have looked into the risk factors for anti-TB DILI. But why some patients develop liver failure, where as the others have a self limiting acute hepatitis is not clear. In the present study we had 35 patients of anti –TB DILI with liver failure which include ALF, SAHF and ACLF. Since it is known that chronic liver disease itself is a risk for developing acute liver failure, we excluded this group while analysing the risk factors for developing liver failure in comparison to acute hepatitis. On multivariate analysis the factors

that predicted liver failure were ,1) duration of ATT more than 5 weeks and 2)continuation of ATT despite having symptoms (p=0.031 and 0.003respectively).There was no difference between the two groups in terms of age, sex , underlying chronic hepatitis ,alcohol consumption. The liver failure group had significantly higher serum bilirubin, lower albumin, as well as prolongation of prothrombin time (p=<0.001 for all variables).

Most of the studies have shown adverse outcome with the presence of encephalopathy, prolongation of prothrombin time. and high bilirubin [15].On comparing the survivor and non survivor groups, on univariate analysis the presence of jaundice, encephalopathy and ascites were significantly more in the non survival groups(p=0.001, <0.001 and 0.03 respectively).Also the non survivor group had significantly more patients who had ATT for more than 5 weeks and were continuing the drug despite symptoms. High serum bilirubin, prolongation of prothrombin time, low albumin and presence of renal failure were all higher in the non survivor group. The average serum bilirubin the non survivor group was 22.2mg/dL (range-3.9-32.8), which supports the Hy's law. There was no significant difference between the two groups in terms of gender or pattern of LFT.

Despite optimal care (short of liver transplantation) majority of patients who came with liver failure due to anti-TB DILI died (20 of 35 patients-57.1%). Björnsson E et al, and O' Grady JG reported older age to be a risk factor for poor outcome in DILI [33,34]. However we have observed a higher mortality in the younger age group In the liver failure group the patients who died were younger compared to those who survived (p=0.04).Also prothrombin time more than 23.3 seconds and MELD score above 23 were associated with mortality (Odds ratio- 11.33,95% CI,2.21-57.87and 21.71,95% CI ,2.28-206.48 respectively).

Conclusion

In conclusion anti-TB DILI with liver failure is associated with high mortality(57.1%).Most common presentation in the liver failure group was SAHF(54.2%).ALF was more common in females and it was associated with very high mortality(88.9%). The presenting symptoms and complications were similar across the liver failure groups with longer hospital stay observed in the SAHF group. Majority of patients who developed anti-TB DILI were on empiric ATT (48.5%) which could have been avoided. Patients who continued ATT despite having hepatitis symptoms and had duration of ATT for more than 5 weeks developed features of liver failure .Over all ,in the liver failure group serum bilirubin more than 13mg/dL, prothrombin time more than 23.3sec and MELD score above 23 were associated with poor outcome. With the DOTS chemotherapy the risk of hepatotoxicity is less. So in future we may come across less number of anti-TB DILI. However in the present study, 4 patients developed liver failure while on DOTS regimen which is a cause for concern.

The future of anti-TB DILI research rests on studies that will help in identifying genetic factors that are associated with susceptibility to serious anti-TB DILI and biomarkers for identifying the development of potentially serious anti-TB DILI in the serum or urine of patients with anti-TB DILI.These might help in decreasing the incidence anti-TB liver failure. Based on the above conclusions the following recommendations can be made:

1) ATT should not be prescribed without objective evidence of tuberculosis.

2) Increased physician and patient awareness is needed in terms of the magnitude and seriousness of anti-TB DILI.

3) Monitoring for symptoms ,and LFT at regular intervals is important, at least for the initial 2 months to pick up early anti-TB DILI and to prevent liver failure deaths.

4) Patients with well compensated chronic liver disease may be initiated on regular ATT but with periodic monitoring of LFT during the treatment period. In those with decompensated chronic liver disease, although there is no clear recommendation, it may be wise to initiate them on non hepatotoxic regimen if clinically indicated.

5) Patients with liver failure due to anti-TB DILI should be referred early to a tertiary centre with facilities for liver transplantation. Considering the scarcity of cadaveric donors in India, live related liver transplantation may merit advice.

Bibliography

[1] Narci C. Teoh, Sleisenger and Fordtran's Gastrointestinal and Liver Disease- Ninth Edition,

[2] Gluud C. Acute, serious drug-induced liver injury J Hepatol. 2002Nov;37(5):675-7.

[3] Einar Björnsson, Drug-induced liver injury: Hy's rule revisited Clin Pharmacol Ther 2006;79:521-8.

[4] Kaplowitz N. Drug-induced liver disorders: implications for drug development and regulation. Drug Saf 2001; 24: 483-90.

[5] Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin LiverDis 2002; 22:145-55.

[6] Haripriya Maddur ,Chalanasi N Idiosyncratic Drug-Induced Liver Injury: A Clinical Update Curr Gastroenterol Rep DOI 10.1007/s11894-010-0154-8

[7] Bjørneboe M, Iversen O, Olsen S. Infective hepatitis and toxic jaundice in a municipal hospital during a five year period: incidence and prognosis. Acta Med Scand 1967; 182:491-501.

[8] Malchow-Møller A, Matzen P, Bjerregaard B, Hilden J, Holst-Christensen J, Staehr Johansen T, et al. Causes and characteristics of 500 consecutive causes of jaundice. Scand J Gastroenterol 1981; 16:1-6.

[9] Whitehead MW, Hainsworth I, Kingham JGC. The causes of obvious jaundice in South West Wales: 2000. Gut 2001; 48:409-13.

[10]. Björnsson E, Ismael S, Nejdet S, Kilander A. Severe jaundice in Sweden in the new millennium: causes, investigations,treatment and prognosis. Scand J Gastroenterol 2003; 38:86-94.

[11]. Victor J. Navarro, Herbal and Dietary Supplement Hepatotoxicity SEMINARS IN LIVER DISEASE/VOLUME 29, NUMBER 4 2009

[12] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States.Ann Intern Med 2002;17;137:947-54.

[13] Wei G, Bergqvist A, Broome U, Björnsson E. Acute liver failure in Sweden: etiology and prognosis [abstract].Scand J Gastroenterol 2004;39 Suppl 240:abstract 48, p 36

[14] Williams R. Classification, etiology, and considerations of outcome in acute liver failure. Semin Liver Dis 1996; 16:343-8.

[15] Ramesh Kumar et al Antituberculosis Therapy–Induced Acute Liver Failure:Magnitude, Profile, Prognosis, andPredictors of Outcome 1HEPATOLOGY, May 2010

[16] Ostapowicz G, Fontana RJ, Schiødt FV, et al; U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002; 137(12):947–954

[17] Harshad Devarbhavi et alSingle-Center Experience With Drug-Induced Liver Injury From India: Causes, Outcome, Prognosis, and Predictors of Mortality Am J Gastroenterol advance online publication, 20 July 2010; doi: 10.1038/ajg.2010.287

[18] Agal S, Baijal R, Pramanik S, Patel N, Gupte P, Kamani P, Amarapurkar D. Monitoring and management of antituberculosis drug induced hepatotoxicity. J Gastroenterol Hepatol. 2005 Nov;20(11):1745-52.

[19] Einar Bjornsson The Natural History of Drug-Induced Liver Injury, SEMINARS IN LIVER DISEASE/VOLUME 29, NUMBER 4 2009

[20] Singla R, Sharma SK, Mohan A, Makharia G, Sreenivas V, Jha B, Kumar S, Sarda P, Singh S Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity. Indian J Med Res. 2010 Jul; 132:81-6.

[21] Be´nichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990;11(2):272–276

[22] Maria VA,Victorino RM.Development and validation of a clinical scale for diagnosis of drug induced hepatitis.Hepatology1997;26(3):664-669

[23] Karen F Murray. Drug related Hepatotoxicity and Acute Liver Failure. Journal of paediatric gastroenterology and nutrition 2008:47; 395-405

[24] Nilesh Mehta, Drug Induced Hepatotoxicity.,e medicine 2009

[25] Stefan Russmann,Pharmacogenetics of Drug-Induced Liver Injury, HEPATOLOGY, Vol. 52, No. 2, 2010

[26] Shapiro MA, Lewis JH Causality assessment of drug-induced hepatotoxicity: promises and pitfalls.. Clin Liver Dis. 2007 Aug;11(3):477-505,

[27] Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States.; Drug Induced Liver Injury Network (DILIN).Gastroenterology. 2008 Dec; 135(6):1924-34, 1934.e1-4

[28] Gupta N K et al,The use of potentially hepatotoxic drugs in patients with liver disease. Aliment Pharmacol Ther 2008

[29] Iba´n˜ez L, Pe´rez E, Vidal X, Laporte JR; Grup d'EstudiMultice`nteric d'Hepatotoxicitat Aguda de Barcelona (GEMHAB). Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolicdiseases: epidemiological and clinical features, and exposureto drugs. J Hepatol 2002;37(5):592–600

[30] R Ramachandran et al. Histological patterns in drug induced liver disease. J clin.Pathol.2009; 62:481-492 .

[31] .Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, et al; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period Gastroenterology. 2005 Aug; 129(2):512-21. Erratum in: Gastroenterology. 2005 Nov; 129(5):1808.

[32] Lee WM, et al Intravenous n-acetylcysteine improves spontaneous survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856-864.

[33] Björnsson E , Olsson R . Outcome and prognostic markers in severe drug induced liver disease. Hepatology 2005 ; 42 : 481 – 9.

[34] O' Grady JG , Graeme GJM , Hayllar KM e t al. Early indicators of prognosis in fulminant hepatic failure . Gastroenterology 1989; 97 : 439 – 45.

[35]David E. Kleiner,Pathology of Drug-Induced Liver Injury,Semin Liver Dis 2009;29:364–372.

[36] World Health Organisation.Global Tuberculosis control:surveillance ,planning ,financing.Geneva,Switzerland:WHO 2008

[37] Jussi J. Saukkonen. An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. Am J Respir Crit Care Med Vol 174. pp 935–952, 2006

[38]Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998Joint Tuberculosis Committee of the British Thoracic Society*Thorax 1998; 53:536–548

[39] Acharya SK, Dasarathy S, Kumer TL, Sushma S, Prasanna KS, Tandon A, Sreenivas V, Nijhawan S, Panda SK, Nanda SK, Irshad M, Joshi YK, Duttagupta S, Tandon RK,

Tandon BN Fulminant hepatitis in a tropical population: clinical course, cause, and early predictors of outcome..Hepatology. 1996 Jun;23(6):1448-55

[40] Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity.

Hepatology. 2001 Jan;33(1):123-30

[41] Alma Tostmann et al Antituberculosis drug-induced hepatotoxicity:Concise up-to-date review Journal of Gastroenterology and Hepatology 23 (2008) 192–202

[42] Steele MA, Burk RF, DesPrez RM.Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest. 1991 Feb; 99(2):465-71.

[43] Thompson NP, Caplin ME, Hamilton MI, Gillespie SH, Clarke SW, Burroughs AK, McIntyre N. Anti-tuberculosis medication and the liver: dangers and recommendations in management. Eur Respir J. 1995 Aug;8(8):1384-8

[44] JN pande et al Risk factors for hepatotoxicity from anti tubeculous treatment.Thorax1996:51,132

[45] Col A C Anand et al. RiskFactors of Hepatotoxicity during Anti Tuberculosis treatment. MJAFI2006;62:45-49

[46] Sarda P Role of acute viral hepatitis as a confounding factor in antituberculosis treatment induced hepatotoxicity. Indian J Med Res. 2009 Jan;129(1):64-7.

[47] Baghaei P, Tabarsi P, Chitsaz E, Saleh M, Marjani M, Shemirani S, Pooramiri MV, Kazempour M, Farnia P, Fahimi F, Mansouri D, Masjedi M Incidence, clinical and epidemiological risk factors, and outcome of drug-induced hepatitis due to antituberculous agents in new tuberculosis cases.. Am J Ther. 2010 Jan-Feb;17(1):17-2

[48] Kishore PV et a Pattern of adverse Drug reactions experienced by Tuberculosis patients in a tertiary care teaching hospital in western Nepal. l.Pak J Pharm Sci,21(1)January 2008; 51-56

[49] Shigeto E; Survey of anti-tuberculosis drug-induced severe liver injury in Japan. Committee for Treatment Japanese Society for Tuberculosis.Kekkaku. 2007 May;82(5):467-7

[50] Makhlouf HA, Helmy A, Fawzy E, El-Attar M, Rashed HA A prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases..Hepatol Int. 2008 Sep;2(3):353-60.

[51] Nash KL, Yeung TM, Lehner PJ, Gibbs P, Griffiths WJ. Orthotopic liver transplantation for subacute hepatic failure following partial treatment of isoniazid-resistant tuberculosis. Transpl Infect Dis. 2008 Jul; 10(4):272-5.

[52] Imogen Mitchell, Wendon J Anti tuberculosis therapy and acute liver failure Lancet 1995;345:555-56

[53] Ichai P, Saliba F, Antoun F, Azoulay D, Sebagh M, Antonini TM, Escaut L, Delvart V, Castaing D, Samuel D. Acute liver failure due to antitubercular therapy: Strategy for antitubercular treatment before and after liver transplantation. Liver Transpl. 2010 Oct;16(10):1136-46

[54]Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR Isoniazid-associated hepatitis in 114 patients. Gastroenterology. 1975 Aug;69(2):289-302.

[55] From the Centers for Disease Control and Prevention. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection--New York and Georgia, 2000. JAMA. 2001 May 23-30;285(20):2572-3.

[56] Juzar Ali Hepatotoxic effects of tuberculosis therapy A practical approach to a tricky management problem..Post grad Med 1996 May: 99(5):217-233

[57] Kishore PV,Drug induced hepatitis with anti-tubercular chemotherapy: challenges and difficulties in treatment. Kathmandu Univ Med J (KUMJ). 2007 Apr-Jun;5(2):256-60.

[58] Jaeschke H, Bajt ML Intracellular signaling mechanisms of acetaminophen-induced liver cell death.Toxicol Sci. 2006 Jan;89(1):31-41. Epub 2005 Sep 21

[59] Kaplowitz N Idiosyncratic drug hepatotoxicity..Nat Rev Drug Discov. 2005 Jun;4(6):489-99.

[60] Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D.Incidence of serious side effects from first-line antituberculosisdrugs among patients treated for active tuberculosis. Am. J. Respir.Crit Care Med. 2003; 167: 1472–7.

[61] van Hest R, Baars H, Kik S et al. Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. Clin. Infect. Dis. 2004; 39: 488–96

[62] Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int. J. Tuberc. Lung Dis. 2002; 6: 699–705.

[63] Fernandez-Villar A, Sopena B, Fernandez-Villar J et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int. J. Tuberc. Lung Dis. 2004; 8:1499–505.

[64] RThiagu et al,Evaluation of patient related risk factors for drug induced hepatotoxicity with anti tubercular chemotherapy in a south Indian tertiarycare hospital..The Journel of Medicine use in Developing countries.2009;1(2):35-45

[65] Lee BH et al,Inactive hepatitis B surface antigen carrier state and hepatotoxicity during antituberculosis chemotherapy. Chest. 2005 Apr;127(4):1304-11

[66]Kaneko Y.etal, Drug-induced hepatotoxicity caused by anti-tuberculosis drugs in tuberculosis patients complicated with chronic hepatitis. Kekkaku. 2008 Jan;83(1):13-9

[67] Bidyut Roy et al, Increased risk of anti tuberculosis drug induced hepato toxicity in individuals with glutathione S transferase M1 null mutation..Jpournel of Gastroenterology and Hepatology(2001)16,1033-1037

[68] Desta Z, Soukhova NV, Flockhart DA. Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: potent inhibition of CYP2C19 and CYP3A. Antimicrob Agents Chemother 2001; 45:382–392.

[69] Tanaka E, Terada M, Misawa S. Cytochrome P450 2E1: its clinical and toxicological role. J Clin Pharm Ther 2000; 25:165–175.

[70] Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, Chang FY, Lee SD. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology. 2002 Apr;35(4):883-9

[71] J Singh,Anti Tuberculosis induced hepatotoxicity :Role of predictive factors..Post grad Med J 1995 71:359-362.

[72] Pachkoria K, Analysis of IL-10, IL-4 and TNF-alpha polymorphisms in drug-induced liver injury (DILI) and its outcome. J Hepatol. 2008 Jul;49(1):107-14.

[73] T.Shanta Devi ,Scientific basis Of DOTS.Tuberculosis control in India

[74] Chang KC, Leung CC, Yew WW, Tam CM.Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter? Eur Respir J. 2007 Feb;29(2):347-51. Sep 27.

[75] Dhingra V.K. Treatment of Tuberculosis in Liver disease. Indian J Tuberculosis .2006:53:232-233

[76] Controlled trial of 4 three-times-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. First report. Hong Kong Chest Service/British Medical Research Council.Lancet 1981;1:171-174

[77] Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, SreenivasV,Singh SSafety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis. 2010 Mar 15;50(6):833-9.

[78] B N Tandon,John O'Grady et al, Recommendations of the International Association for the Study of the Liver Subcommittee on nomenclature of acute and subacute liver failure1Journal of Gastroenterology and Hepatology (1999) 14, 403–40

[79]Shiv Kumar Sarin,et al ACUTE ON CHRONIC LIVER FAILURE (ACLF): CONSENSUS RECOMMENDATIONS OF THE ASIAN PACIFIC ASSOCIATION FOR THE STUDY OF THE LIVER (APASL).

[80] Moises Ilan Nevah,Michael B. Fallon ,Sleisenger and Fordtran's Gastrointestinal and Liver Disease .Ninth Edition.

[81] Ormerod LP,et al Hepatotoxicity of anti tuberculous drugs .Thorax 1996;51:111-3

[82] Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculosis therapy: clinical profile and reintroduction of therapy. J Clin Gastroenterol 1996; 22:211-214.

[83] Sharma et al,Acute viral hepatitis as a confounding factor in patients with antituberculosis treatment induced hepatotoxicity. Indian J Med Res 130, August 2009, pp 200-201

[84] TM O'Connell et al ,The Application of Metabonomics to Predict Drug-Induced Liver Injury Clinical pharmacology & Therapeutics | VOLUME 88 NUMBER 3 | september 2010

[85] Purabi Deka Bose et al,Role of polymorphic N-acetyl transferase2 and cytochrome P4502E1 gene in antituberculosis treatment-induced hepatitis Journal of Gastroenterology and Hepatology 26 (2011) 312–318 .

Anti-TB DILI Proforma

Name

Age

Sex

Reason for ATT – Empirical

PTB

Extra Pulmonary

ATT Regimen

Duration of ATT

Continuation of ATT despite symptoms Y/N

Onset of symptoms A symptomatic

Symptoms –

RUQ abdominal Pain Y/N

Jaundice, Y/N

Anorexia Vomiting, Y/N

Fever Y/N

Skin rash Y/N

Arthralgia. Y/N

Interval between Jaundice to Encephalopathy

Use of Alternative treatment

Addictions – Ethanol/ Smoking

Co morbidities – DM/HT// Underlying CLD/Ch Hepatitis

Past h/o of DILI Y/N

Clinical

Nutritional status-Ht Wt BMI

General Examination

Systemic Examination

Grade of encephalopathy

Laboratory Values

LFT – Baseline Abnormal Follow up

LFT Pattern Hepato cellular / Cholestatic/ or mixed

PT/INR

APTT

Plasma Glucose

BBVS

IgM HAV / HEV

ANA

S.ceruloplasmin

Immunoglobulin

Absolute eosinophil count

Imaging USG/CT abdomen

Histology

Outcome : Survived/Death/Liver Transplantation

RUCAM score:

Consent Form

I understand that Dr. .....is doing a study to assess the risk factors, prognostic factors and outcome in ATT induced Hepatitis. The study involves being interviewed (about the disease) and following up test reports done as part of your clinical care. The results of the test done in connection with the study may not directly benefit me. They are likely to indirectly benefit other patients with the disease.

I understand that my withdrawal from the study, at any time will not affect the treatment being given.

Study Title: Clinical profile, prognostic factors and outcomes in anti Tuberculous drug induced liver injury'

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission

to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____